Proposed Re-evaluation Decision PRVD2011-09

Propoxur

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Overview

Proposed Re-evaluation Decision for Propoxur

After a re-evaluation of the insecticide propoxur, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing continued registration of some propoxur uses in Canada and the phase-out of uses with risk concerns.

An evaluation of available scientific information found that under the proposed conditions of use, some uses of products containing propoxur have value and do not present unacceptable risks to human health or to the environment. These uses include indoor crack and crevice applications of Commercial class products and outdoor uses of Domestic and Commercial class products, as well as bait trays. As a condition of continued registration of these uses, new risk-reduction measures are proposed and additional data are required.

Certain uses of propoxur are proposed for phase-out because registrants do not support continued registration or because of the human health risks. These are: use to control biting flies including mosquitoes, black flies, sandflies and punkies, pet collars, and all indoor uses of Domestic class products except bait trays.

To address some of the uncertainties in the risk assessment for the indoor uses of Domestic class products, it is possible that additional data and use information could be submitted. Any relevant information provided during the Proposed Re-evaluation Decision consultation period will be considered prior to a final decision.

The PMRA's pesticide re-evaluation program considers potential risks as well as the value of pesticide products to ensure they meet modern standards established to protect human health and the environment. Regulatory Directive DIR2001-03, *PMRA Re-evaluation Program*, presents the details of the re-evaluation activities and program structure. Re-evaluation draws on data from registrants, published scientific reports, information from other regulatory agencies and any other relevant information available.

This proposal affects all end-use products containing propoxur registered in Canada. Once the final re-evaluation decision is made, registrants will be instructed on how to address any new requirements.

This Proposed Re-evaluation Decision is a consultation document[1] that summarizes the science evaluation for propoxur and presents the reasons for the proposed re-evaluation decision. It also proposes additional risk-reduction measures to further protect human health and the environment.

[1] Consultation statement as required by subsection 28(2) of the *Pest Control Products Act*.

The information is presented in two parts. The Overview describes the regulatory process and key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessment of propoxur.

The PMRA will accept written comments on this proposal up to 60 days from the date of publication of this document. Please forward all comments to Publications (see contact information on the cover page of this document).

What Does Health Canada Consider When Making a Re-evaluation Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[2] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions or proposed conditions of registration. The Act also requires that products have value[3] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies hazard and risk assessment methods as well as policies that are rigorous and modern. These methods consider the unique characteristics of sensitive subpopulations in both humans (for example, children) and organisms in the environment (those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties present when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Health Canada's website at healthcanada.gc.ca/pmra.

Before making a final re-evaluation decision on propoxur, the PMRA will consider all comments received from the public in response to this consultation document.[4] The PMRA will then publish a Re-evaluation Decision[5] on propoxur, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and the PMRA's response to these comments.

For more details on the information presented in this overview, please refer to the Science Evaluation of this consultation document.

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2 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

3 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and (c) health, safety and environmental benefits and social and economic impact".

4 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

5 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

What Is Propoxur?

Propoxur is a non-systemic carbamate insecticide used to control a broad range of insect and arthropod pests on a wide variety of sites including: structures (indoors and outdoors), transportation vehicles (for example, boats, ships, trucks, trains, etc.), on companion animals, in human habitat and recreational areas (for biting fly and mosquito control) and in residential outdoor areas. Propoxur is not currently registered in Canada to control bed bugs.

Propoxur is applied by both ground and aerial means, using mist blowers, foggers and ultra low volume application equipment to control mosquitoes and other biting flies. Cats and dogs are treated using slow release pet collars. Propoxur is also applied to other sites using pressurized spray cans, hand held and backpack sprayers, paste applicators and foggers by professional applicators and casual users such as home owners.

Health Considerations

Can Approved Uses of Propoxur Affect Human Health?

Risks of concern were identified for residential exposure to propoxur. For all indoor use scenarios, there are cancer risks for all age groups from postapplication exposure of propoxur and there are non-cancer postapplication risks for children.

Potential exposure to propoxur may occur through the diet, when handling and applying the product, or when entering or contacting treated sites. When assessing health risks, two key factors are considered: the levels at which no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose at which no effects are observed.

A single high dose of propoxur caused high oral toxicity, low dermal toxicity, and slight inhalation toxicity. Propoxur was a non- or mild eye irritant, and it was not a skin irritant or sensitizer. Acute overexposure to propoxur can inhibit cholinesterase, an enzyme necessary for normal functioning of the nervous system. Clinical signs typical of cholinesterase inhibition were observed by all routes of exposure in acute toxicity studies and included tremors, shortness of breath, salivation, and apathy. The onset of neurotoxicity was rapid but the effects were transient. No pronounced gender differences were noted in the database.

The first signs of toxicity in animals given daily oral doses of propoxur over longer periods of time were cholinesterase inhibition or liver toxicity. Propoxur was not toxic by the dermal route in short-term studies. Cholinesterase inhibition was the most sensitive endpoint in repeated dose inhalation studies. The severity of neurotoxicity increased with repeated inhalation but not repeated oral dosing.

There was evidence of urinary bladder and liver carcinogenicity after long-term oral or inhalation exposure. The genotoxicity data for propoxur yielded both positive and negative results. Supplementary evidence in public literature suggests that propoxur can suppress the immune system.

There was no evidence of increased susceptibility of the young in reproduction or developmental toxicity studies, although cholinesterase inhibition was not measured in the young. In reproductive studies, maternal cholinesterase activity was the most sensitive endpoint. When pregnant animals were orally exposed to propoxur, in cases where propoxur caused effects in the developing young, the effects on the developing fetus were only observed at doses that caused death in the mother. The assessment protects against these effects, by establishing an acceptable level of risk.

Occupational Risks from Handling Propoxur

Occupational non-cancer and cancer risks are not of concern, provided that risk mitigation measures are implemented.

For commercial applicators or pest control operators (PCOs) applying propoxur products, the calculated inhalation Margin of Exposures (MOEs) exceed the target MOE for almost all scenarios using baseline personal protective equipment (PPE) and are not of concern. One exception is high pressure handwand application of emulsifiable concentrate and solutions. However, the calculated inhalation MOEs for high pressure handwand exceed the target MOE and are not of concern, provided that baseline PPE is worn during handling and a respirator is worn if more than 8 kg a.i. is handled per day.

The calculated dermal and inhalation cancer risks are below the occupational threshold of 1×10^{-5} for most scenarios using baseline PPE and are not of concern. One exception is high pressure handwand application of emulsifiable concentrate and solutions. The calculated dermal and inhalation cancer risks for high pressure handwand are not of concern provided that baseline PPE is worn during handling, a respirator is worn if more than 8 kg a.i. is handled in one day, and no more than 14 kg a.i. is handled in one day.

Occupational non-cancer risks are not of concern for postapplication workers. Occupational cancer risks for postapplication workers are of concern.

For workers entering treated sites, a specific postapplication assessment was not conducted. It was assumed that risks to postapplication workers would be similar to or less than residential postapplication risks. As cancer risks were identified for postapplication residential scenarios, there is also cancer concern for postapplication workers.

To minimize potential exposures for indoor crack and crevice applications of Commercial Class products, pressurized products must be applied with a straw applicator, whereas products formulated as emulsifiable concentrates or solutions must be applied using a low pressure sprayer equipped with a pin stream nozzle to direct sprays into cracks and crevices. Also, the directions for use must be modified to provide specific instructions for crack and crevice application.

Risks in Residential and Other Non-Occupational Environments

Residential handler non-cancer and cancer risks are not of concern.

For homeowners applying Domestic class products, the calculated inhalation MOEs are greater than the target MOE for all residential applicator exposure scenarios and are not of concern.

The calculated dermal and inhalation cancer risks are below the residential threshold of 1×10^{-6} for all residential applicator exposure scenarios and are therefore not of concern.

Residential non-cancer risks from certain postapplication exposures to children are of concern due to the potential for incidental oral exposure of propoxur.

For children mouthing an object that has come in contact with a treated surface associated with crack and crevice applications, the calculated incidental oral MOEs are greater than the target MOE. However, for treated surface-to-hand-to-mouth exposures associated with indoor crack and crevice applications, and pet-to-hand-to-mouth exposures associated with pet collar applications, achieved MOEs are below the target MOE and are of concern.

To minimize potential exposures for indoor crack and crevice applications of Commercial Class products, pressurized products must be applied with a straw applicator, whereas products formulated as emulsifiable concentrates or solutions must be applied using a low pressure sprayer equipped with a pin stream nozzle to direct sprays into cracks and crevices. Also, the directions for use must be modified to provide specific instructions for crack and crevice application.

For indoor postapplication exposure, the calculated inhalation MOEs are greater than the target MOE for all residential postapplication exposure scenarios and are not of concern.

There are no risk concerns for residential bait tray and outdoor postapplication exposure to propoxur. Outdoor residential crack and crevice, structural and stinging insect nest treatments are limited to areas not frequented by, or that are inaccessible to children. Therefore, the potential for postapplication exposure is minimal. Bait tray application and postapplication exposure was considered to be negligible because the active ingredient is enclosed in a self-contained unit and is not available for exposure.

Indoor residential cancer risks for postapplication exposure are of concern for most uses.

The majority of calculated oral, dermal and inhalation cancer risks are above the threshold of 1×10^{-6} for all residential postapplication exposure scenarios and are of concern.

To minimize potential exposures for indoor crack and crevice applications of Commercial Class products, pressurized products must be applied with a straw applicator, whereas products formulated as emulsifiable concentrates or solutions must be applied using a low pressure sprayer equipped with a pin stream nozzle to direct sprays into cracks and crevices. Also, the directions for use must be modified to provide specific instructions for crack and crevice application.

There are no cancer risk concerns for indoor residential bait tray postapplication exposure to propoxur.

Residues in Food and Drinking Water

Dietary risks from food and drinking water are not of concern.

Reference doses define levels to which an individual can be exposed over a single day (acute) or lifetime (chronic) and expect no adverse health effects. Generally, dietary exposure from food and drinking water is acceptable if it is less than 100% of the acute reference dose or chronic reference dose (acceptable daily intake). An acceptable daily intake is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects.

Exposure for all Canadians through drinking water is minimal since propoxur is mainly used indoors. The only registrant-supported outdoor uses are structural applications to the perimeter of buildings. This indicates that the exposure of environmental compartments such as surface and drinking water to propoxur will be minimal.

Although propoxur is not applied directly to crops, human exposure to propoxur was estimated from residues in food commodities, resulting from exposure in treated areas (for example, food handling establishments). This exposure to propoxur represents approximately 4% of the acute reference dose and 2% of the chronic reference dose for the most highly exposed subpopulation of infants less than 1 year old, and is not of concern (refer to Appendix VI). The cancer risk was 2×10^{-7} for the general population and is not of concern (refer to Appendix VI). A lifetime cancer risk that is at or below 1×10^{-6} (1 in a million) usually does not indicate a risk concern for the general population when exposure occurs through pesticide residues in/on food and drinking water, and to otherwise unintentionally exposed persons. Further information on how the potential cancer risks from pesticides are assessed can be found in *A Decision Framework for Risk Assessment and Risk Management in the Pest Management Regulatory Agency* (SPN2000-01).

The *Food and Drugs Act* prohibits the sale of adulterated food; that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act (PCPA)*. Each MRL value defines the maximum concentration in parts per million (ppm) of a pesticide allowed in/on certain foods. Food containing a pesticide residue that does not exceed the established MRL does not pose a health risk concern.

No Canadian MRLs have been established for propoxur residues in/on any commodity. Where no specific MRL has been established, a default MRL of 0.1 ppm applies, which means that pesticide residues in a food commodity must not exceed 0.1 ppm. However, changes to this general MRL may be implemented in the future, as indicated in Information Note: Progress on Minimizing Reliance on the 0.1 Parts per Million as a General Maximum Residue Limit for Food Pesticide Residue, December 2009.

Environmental Considerations

What Happens When Propoxur Is Introduced into the Environment?

Propoxur does not pose a potential risk to terrestrial and aquatic organisms since, based on the use pattern, the environmental exposure is expected to be negligible. Additional risk-reduction measures are not needed.

If propoxur is released into the environment some of it can be found in soil and surface water. Propoxur is moderately persistent to persistent with the main route of dissipation being biotransformation in soil. Propoxur is not expected to volatilize significantly. Propoxur is mobile in soil. Therefore, there is a potential for propoxur to move to groundwater and surface water, if propoxur was registered for significant outdoor use.

Propoxur would pose a risk to terrestrial and aquatic organisms if there was environmental exposure. However, the use pattern indicates that potential exposure of non-target organisms is expected to be minimal.

Value Considerations

What Is the Value of Propoxur?

Propoxur is registered in Canada for the control of a wide spectrum of pests on a large number of sites.

In Canada, propoxur is registered to control a wide range of insect and arthropod pests such as: ants, beetles, cockroaches, flies, fleas, millipedes, mites, mosquitoes, spiders, sow bugs, ticks, wasps, and other insect pests on the following sites:

- on and in structures (commercial, industrial, institutional and residential);
- in transportation vehicles such as ships, trains, trucks, etc.;
- in outdoor residential sites;
- on companion animals (cats and dogs); and
- in human habitats and recreational sites to control black flies and mosquitoes.

Excluding fumigants, there are few alternative active ingredients to propoxur registered in Canada with a broad spectrum of control of structural pests. Such active ingredients include silicon dioxide (diatomaceous earth and silica aerogel), boric acid and synthetic pyrethroids.

Propoxur is important for the purpose of resistance management of structural insect pests.

Propoxur's broad spectrum of control of insects and arthropods makes it valuable as an alternative active ingredient to the synthetic pyrethroids (resistance mode of action (MoA) group 3 insecticides), which are also registered for the control of a wide range of structural pests and account for the majority of products registered in Canada for this use.

Propoxur is a MoA group 1A insecticide. In recent years, the registrations of several carbamate and organophosphate insecticides (MoA group 1A and 1B insecticides, respectively) that were used within structures have been discontinued (for example, bendiocarb, chlorpyrifos, diazinon) or their use patterns have been amended, limiting their use to specific sites or to specific application methods (for example, dichlorvos, propetamphos). Other organophosphate active ingredients registered for use on structural sites are currently under re-evaluation, for example malathion. This limits the availability of active ingredients from MoA groups 1A and 1B to rotate with the synthetic pyrethroids (MoA group 3 insecticides) leading to the potential for limited resistance management options.

Propoxur is characterized as providing rapid knockdown and has a long residual action.

Knockdown, which is characterized as an insect's inability to walk or fly, is rapid with propoxur. Residual action allows propoxur to continue to kill insect pests even after the spray has dried. These traits are important for the control of public health pests such as mosquitoes and cockroaches where immediate and prolonged reduction of a pest population is required.

Alternative active ingredients are available for mosquito control and the pet collar uses of propoxur.

Mosquito control includes the use of pesticides to control the larval and adult stages. Alternative active ingredients to propoxur are available in Canada for the control of mosquito larvae and adults.

Alternative active ingredients to propoxur are available in Canada for the control of fleas and ticks on cats and dogs. These include active ingredients formulated into pet collars and shampoos. Veterinary drugs are also available for control of fleas and ticks on dogs and fleas on cats.

Measures to Minimize Risk

Notwithstanding uncertainties in the risk assessment, there is a high level of concern for pet collar and indoor uses of Domestic class products containing propoxur, excluding bait trays. All pet collar and indoor uses of Domestic class products containing propoxur (except bait trays) are proposed for phase out since, based on available scientific information, they do not meet Health Canada's current standards for human health protection. Additional mitigation measures are not feasible.

Registered pesticide product labels include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

Risk-reduction measures are being proposed to address potential risks identified in this assessment. These measures, in addition to those already identified on existing propoxur product labels, are designed to further protect human health and the environment. The following additional key risk-reduction measures are being proposed.

Additional Key Risk-Reduction Measures

Human Health

a) To protect commercial mixers, loaders, and applicators: The use of additional protective equipment and limits on the amount of active ingredient handled per day are proposed.
b) To protect residents and workers entering treated sites: specific application equipment and use directions on Commercial class product labels are proposed.
c) To protect residents and homeowners: it is proposed that all indoor uses of Domestic class products be discontinued, except bait trays.
d) To protect homeowners/pet owners: it is proposed that all pet collar products be discontinued.

Proposed label amendments to be implemented are found in Appendix XII.

What Additional Scientific Information Is Requested?

Human Health

The human health risks were found to be acceptable for certain uses of propoxur with the addition of mitigation measures. However, since risk concerns were identified for indoor residential postapplication exposure, the following information is required as a condition of continued registration under section 12 of the *Pest Control Products Act* to address uncertainties in the risk assessment.

Toxicology

DACO: 4.5.12 There was no sensitivity of the young demonstrated in the database, but an acute comparative cholinesterase study (juvenile versus adult animals) in rats is required due to the neurotoxic potential of propoxur to adults.

Occupational and Residential Exposure

DACO 5.2 Application rates in g a.i/cm^2 for all Commercial products

- Area treated per day (ATPD) for commercial application using paintbrush and aerosols.
- Treatment frequency (number of days of exposure per year) for commercial applicators.
- Working duration for pesticide control operators.

DACO 5.9 Indoor transferable residue and dissipation data following crack and crevice application in residential scenarios based on the Canadian use pattern (application rates). This study methodology needs to be consistent with the transfer coefficient in the USEPA Residential Standard Operating Procedures (SOPs).

DACO 5.10 Indoor air monitoring data and dissipation data following crack and crevice application based on the Canadian use pattern (application rates).

Next Steps

Before making a re-evaluation decision on propoxur, Health Canada's Pest Management Regulatory Agency will consider all comments received from the public in response to this consultation document. The PMRA will then publish a Re-evaluation Decision, which will include the decision, the reasons for it, a summary of comments received on the proposed decision and the PMRA's response to these comments.

Registrants and the public are asked to submit supplementary information to confirm or refine the current risk assessment, including:

- Quantitative and/or qualitative information on the economic and social importance of propoxur for various registered uses; and
- Feedback on the viability of alternative chemical and non-chemical pest management practices for the registered site and pest combinations.

Other Information

At the time that the re-evaluation decision is made, the PMRA will publish an Evaluation Report on propoxur in the context of this re-evaluation decision (based on the Science Evaluation of this consultation document). In addition, the test data on which the decision is based will also be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa, Ontario, Canada).

Science Evaluation

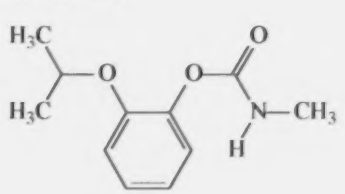
1.0 Introduction

Propoxur is a broad spectrum, non-systemic, resistance management Mode of Action (MoA) Group 1A insecticide, which inhibits the enzyme acetylcholinesterase, thus interrupting the transmission of nerve impulses. It works by contact and stomach action. Propoxur is applied by both ground and aerial means using mist blowers, foggers and ultra low volume application equipment to control mosquitoes and other biting flies. Cats and dogs are treated using slow release pet collars. Propoxur is also applied to other sites using pressurized spray cans, hand held and back pack sprayers, paste applicators and foggers by professional applicators and casual users such as home owners.

Following the re-evaluation announcement for propoxur, McLaughlin Gormley King Company, the registrant of the technical grade active ingredient (TGAI) and primary data provider in Canada, indicated continued support of all uses included on the labels of Commercial Class and Domestic Class end-use products (EPs), except the use to control biting flies including mosquitoes, black flies, sandflies and punkies.

2.0 The Technical Grade Active Ingredient, Its Properties and Uses

2.1 Identity of the Technical Grade Active Ingredient

Common name		Propoxur
Function		Insecticide
Chemical Family		Carbamate
Chemical name		
1	**International Union of Pure and Applied Chemistry (IUPAC)**	2-isoproproxyphenyl methylcarbamate
2	**Chemical Abstracts Service (CAS)**	2-(1-methylethoxy)phenyl methylcarbamate
CAS Registry Number		114-26-1
Molecular Formula		$C_{11}H_{15}NO_3$
Structural Formula		
Molecular Weight		209.24

Purity of the Technical Grade Active Ingredient	96% minimum
Registration Number	18277

Identity of relevant impurities of human health and environmental concern:

Based on the manufacturing process used, impurities of human health or environmental concern as identified in the Canada Gazette, Part II, Vol. 142, No. 13, SI/2008-67 (2008-06-25), including TSMP Track 1 substances, are not expected to be present in the product.

2.2 Physical and Chemical Properties of the Technical Active Ingredient

Property	Result
Vapour pressure at 25°C	2.8 mPa
Ultraviolet (UV)/visible spectrum	Not applicable
Solubility in water at 20°C	1.75 g/L
n-Octanol–water partition coefficient	log K_{ow} =1.56
Dissociation constant	Not applicable

2.3 Description of Registered Propoxur Uses

Appendix I lists all products containing propoxur that are currently registered as of January 28, 2009 under the authority of the *Pest Control Products Act*. Appendix IIa lists all Commercial Class uses for which propoxur was registered as of December 22, 2008, while Appendix IIb lists all Domestic Class uses for which propoxur was registered as of January 28, 2009.

Not all uses presently registered are supported by the registrant, as indicated in Appendices IIa and IIb. Only uses of propoxur that were supported by the registrant have been considered in the health and environmental risk assessments.

Uses of propoxur belong to the following use-site categories: structural, companion animals, human habitat and recreational areas, and residential outdoors.

3.0 Impact on Human Health and Animal Health

Toxicology studies in laboratory animals describe potential health effects resulting from various levels of exposure to a chemical and identify dose levels at which no effects are observed. Unless there is evidence to the contrary, it is assumed that effects observed in animals are relevant to humans and that humans are more sensitive to effects of a chemical than the most sensitive animal species.

3.1 Toxicological Summary

A detailed review of the toxicological database for propoxur (2-isopropoxyphenyl-N-methylcarbamate) was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to this chemical pest control product.

Following oral ingestion, propoxur was rapidly absorbed, metabolized and excreted, regardless of the duration of dosing. In the rat, propoxur was primarily distributed to the kidneys and also to the liver, small intestine, blood, and lymph fluid. With repeated dosing, propoxur persisted in the kidneys. For the most part, propoxur was rapidly excreted in urine in free form and as glucuronide and sulphate conjugated metabolites, but propoxur was also excreted in lesser amounts via expired air and faeces. The metabolic pathways of propoxur in mice, rats, hamsters, and monkeys were similar and included hydrolysis of the ester bond, N-methyl hydroxylation and demethylation, and ring hydrolysis. There were no gender or species differences in the identity of the major metabolites, although ring hydroxylation at positions 3, 4, and 5 occurred in rats and hamsters, but hydroxylation at positions 4 and 5 only were observed in monkeys. Analysis of urine from a human who intentionally ingested a propoxur formulation suggested that the metabolic pathway of propoxur in humans is similar to that observed in the animal studies. The primary metabolites were less toxic than propoxur in acute oral toxicity tests and were mostly non-genotoxic.

Similar to other carbamates, the main endpoint of concern for propoxur was brain, erythrocyte, and plasma cholinesterase inhibition. Clinical signs typical of cholinesterase inhibition were observed by all routes of exposure in acute toxicity studies and included muscle fasciculations, convulsions, dyspnoea, salivation, bristling coat, and apathy. Propoxur exhibited high oral toxicity in the rat, low dermal toxicity in the rat and rabbit, and slight inhalation toxicity in the rat. Propoxur was a mild or a non-irritant to rabbit eyes, a dermal non-irritant in rabbits and a dermal non-sensitizer in guinea pigs.

In dogs and rats, treatment-related effects of short-term exposure to propoxur included clinical chemistry changes indicative of liver damage, increased liver weight and decreased body weight gain. This suggests that liver toxicity was the most sensitive endpoint, although cholinesterase inhibition was not assessed in all studies. Hematological changes were observed in a dog study of longer duration and at the highest dose tested there were clinical signs of neurotoxicity and mortality. In comparison, subchronic gavage doses of propoxur in monkeys produced only clinical signs of neurotoxicity. There were no significant gender differences noted. Together this suggests that dogs are the most sensitive and monkeys are the least sensitive to liver effects by the oral route. No dermal toxicity was observed following repeated applications in rabbits.

Neurotoxicity studies in the rat demonstrated rapid onset of both clinical neurological symptoms and cholinesterase inhibition. They were both directly related to dose levels but unrelated to gender. Duration of dosing by the oral route was unrelated to the severity of effects, which is consistent with the rapid and transient metabolism of propoxur. In comparison, there was an increase in severity of neurotoxicity with chronic dosing by the inhalation route. The neurotoxic effects of propoxur may be greater in rats than dogs or monkeys. A supplemental tolerance study in mice suggested that repeated exposure to propoxur does not directly affect cholinergic receptors, but may indirectly increase liver metabolism. Neuropathy was not considered to be an endpoint of concern, for slight sciatic nerve neuropathy was only observed at a toxic dose in a chronic dietary/carcinogenicity rat study. Supplementary data from humans suggested exposure caused rapid and transient cholinergic inhibition and symptoms similar to effects observed in animal studies.

Studies for chronic toxicity/carcinogenicity demonstrated that propoxur could lead to a time and dose-dependent progression of urinary bladder carcinomas in rats of both sexes, as well as hepatocellular adenomas in males. However, it was noted with oral dosing that urinary bladder papillomas and carcinomas were seen at or above levels causing toxicologically significant decreased body weight gain in rats and that hyperplasia was reversible with time. There were no strain differences between Wistar and Sprague-Dawley rats in hyperplasia incidence. Mice also developed urinary bladder hyperplasia and hepatocellular adenomas but at higher dietary doses than in rats, suggesting that mice are susceptible but less sensitive to the neoplastic effects of propoxur than rats. In contrast, hamsters and dogs were refractory to propoxur-induced hyperplasia. Urinary bladder papillomas and carcinomas in both sexes were observed following chronic inhalation of propoxur in rats. The increase was very slight and not statistically significant. An increase in hepatocellular adenomas in males was also noted along with equivocal evidence of uterine adenocarcinomas in females. Increases in uterine carcinomas were also produced in an oral carcinogenicity study in rats, although the incidences were within historical control levels. A two-stage mouse model of skin carcinogenicity from open literature suggested that propoxur acts as a tumor promotor, which is consistent with the reversibility of urinary bladder hyperplasia. This also revealed that propoxur can induce neoplasm through a dermal route of administration, thus propoxur can produce neoplasia through all routes of exposure.

Propoxur was examined for mutagenicity in many studies. Propoxur was not mutagenic in bacteria in vitro, nor did it increase unscheduled DNA synthesis in rat hepatocytes in vitro or urinary bladder epithelial cells in vivo, even when urinary bladder hyperplasia was observed. Propoxur increased DNA damage of single lymphocyte cells in a supplementary in vitro Comet assay. Overall the weight of evidence was that propoxur was not mutagenic. Evidence for clastogenicity was mixed. Propoxur was not clastogenic in two in vitro and three in vivo chromosome aberration tests, and an in vivo micronucleus assay in mouse bone marrow cells. In contrast, two in vivo micronucleus assays indicated that propoxur was clastogenic, perhaps because of later sampling timepoints or higher dose levels. Additionally, in supplementary in vitro sister chromatid exchange studies comparing propoxur with nitrosopropoxur, propoxur was clastogenic in human lymphocytes but not clastogenic or genotoxic in respiratory cell lines. The latter study also suggested propoxur inhibited gap-junctional intercellular communication as a

possible way that propoxur promotes neoplasia. The weight-of-evidence demonstrates that propoxur is not mutagenic but may be clastogenic in mammalian cells.
In reproductive and developmental studies, offspring were equally or less sensitive to propoxur than maternal animals. In multigenerational reproductive studies in rats, maternal cholinesterase inhibition was the most sensitive endpoint, although cholinesterase inhibition was not measured in offspring. Reproductive effects included decreased pup birth weight, number of implantations per dam and number of pups per dam. Offspring effects were limited to decreased pup weight gain and viability. Developmental toxicity studies with propoxur in mice, rats and rabbits provided no evidence of teratogenicity and no additional sensitivity of the fetus with in utero exposure. In cases where propoxur caused effects in developing young, the effects on the developing fetus were only observed at doses that caused death in the mother. Maternal rabbits exposed to propoxur were slightly less sensitive than rats to clinical symptoms, decreased weight gain and food consumption, but rabbit offspring were more sensitive to developmental effects (slight post-implantation loss, a decreased number of pups per dam, slight ossification delay). There was no evidence of endocrine disruption.

Supplemental immunotoxicity studies from public literature suggest that propoxur is an immunosuppressant. In mice and rats, propoxur induced dose-dependent decreases in serum antibody titre and IgM-plaque-forming cell counts, suggesting effects on humoral-mediated immunity. Rats exposed to propoxur also exhibited reduced delayed type hypersensitivity responses suggestive of effects on cell-mediated immunity. Propoxur has been shown to be distributed through the lymphoid system in rats and may increase the susceptibility to cancer through immunosuppression.

Although *N*-nitrosopropoxur is mutagenic and clastogenic in vitro, there is no evidence that it forms in vivo. Dietary ingestion of propoxur can produce low levels of a nitrosated urinary compound, but it is not *N*-nitrosopropoxur. Propoxur nitrosated with sodium nitrate is mutagenic in vitro but it is not clastogenic in vivo. Moreover, the addition of sodium nitrate did not increase the incidence of urinary bladder hyperplasia in propoxur treated rats in a subchronic dietary study, suggesting that nitrosation does not enhance tumorigenicity. Thus overall there is a low level of concern for genotoxicity or tumorigenicity due to nitrosation of propoxur.

Reference doses have been set based on No Observed Adverse Effect Levels NOAELs or Lower Confidence Limits on the Benchmark Dose (BMDLs) for the most sensitive indicator of toxicity. These reference doses incorporate various uncertainty factors to account for extrapolating between rats and humans and for variability within human populations.

In assessing the occupational, residential, and dietary risks from potential exposure to propoxur products, the standard uncertainty factor (UF) of 100 has been applied to account for interspecies extrapolation and intraspecies variability.

Results of the acute and repeated-dose tests conducted on laboratory animals with propoxur, along with the toxicology endpoints for use in the human health risk assessment, are summarized in Tables 1 and 2 of Appendix IV.

3.1.1 PCPA Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, as well as potential pre- and post-natal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database, prenatal developmental toxicity studies were available in mice, rats and rabbits (one study in mice, two studies in rats, three studies in rabbits). There were also two-generation reproduction studies in rats (two studies).

With respect to potential pre-and post-natal toxicity, offspring were equally or less sensitive to propoxur than maternal animals in the available studies. Maternal cholinesterase inhibition was the most sensitive endpoint in reproduction or developmental studies, although cholinesterase inhibition was not measured in offspring or fetuses. In a 2-generation dietary reproduction study in rats, reproductive effects (decreased pup birth weight, number of implantations per dam and number of pups per dam) and offspring effects (decreased pup weight gain and viability) only occurred in the presence of parental toxicity (cholinesterase inhibition, decreased body weight). In another 2-generation dietary reproduction study in rats with lower dose levels, there were no reproductive or offspring effects. Developmental toxicity studies with propoxur in mice, rats and rabbits provided no evidence of teratogenicity or sensitivity of the fetus with in utero exposure. In mice, fetal mortality and decreased fetal weight were observed, but only at greater doses than that which produced an increase in maternal mortality. No developmental effects were observed in rats. Developmental effects were only observed in one of three rabbit studies (slight post-implantation loss, a decreased number of pups per dam, slight ossification delay), but these effects occurred in the presence of maternal mortality. Thus no sensitivity of the young was identified in developmental or reproduction studies.

The risk assessment for sensitivity to cholinesterase inhibition cannot be refined due to a lack of cholinesterase measurements in the young. Thus an acute comparative cholinesterase assay (assessment of cholinesterase activities in young and adult animals by the oral route) is required to refine the toxicology risk assessment. On the other hand, sensitivity of the young to other endpoints was not demonstrated in the toxicological database, which included several developmental and reproductive toxicity studies. On the basis of this information, the PCPA factor was reduced to one-fold.

3.2 Occupational and Non-Occupational Risk Assessment

Occupational and non-occupational risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating uncertainty factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects. However, MOEs less than the target MOE require measures to mitigate (reduce) risk.

3.2.1 Toxicology Endpoint Selection for Occupational and Non-Occupational Risk Assessment

3.2.1.1 Dermal endpoint

A subchronic dermal study in rabbits is considered the most appropriate study for dermal risk assessments of all durations, since the effect of propoxur on cholinesterase levels is rapid and transient, suggesting that duration does not impact toxicity. However, no treatment-related effects were observed, including effects on cholinesterase activity, up to the limit dose of 1000 mg/kg bw/day. As this study is considered protective of other endpoints of concern in the database, a quantitative assessment for non-cancer endpoints is not required for dermal risk assessments.

3.2.1.2 Short- and intermediate-term inhalation endpoints

The NOAEL of 0.010 mg/L, equivalent to 2.6 mg/kg bw/day, from a 4-week inhalation toxicity study was chosen for the short- and intermediate-term inhalation risk assessments. Brain and plasma cholinesterase inhibition occurred at the LOAEL of 0.047 mg/L, or 13 mg/kg bw/day. This LOAEL is consistent with another 4-week inhalation study where brain cholinesterase inhibition occurred at 0.045 mg/L in female rats, as well as the 4-week interim measurement from a 12-week inhalation study that showed depressed erythrocyte cholinesterase levels in female rats at 0.032 mg/L, or 8.6 mg/kg bw/day. The target MOE is 100, accounting for standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. For the residential risk assessment, the PCPA factor can be reduced to 1-fold based on the rationale provided in Section 3.1.1 PCPA Hazard Consideration, also resulting in an overall target MOE of 100. This target MOE is considered protective of all populations, including pregnant women and their children.

3.2.1.3 Non-dietary (incidental) oral endpoint(s)

For non-dietary (incidental) oral exposure (up to 6 months), the selected toxicological endpoint is the same as for the Acute Reference Dose (ARfD) and Acceptable Daily Intake (ADI) determination (refer to Sections 3.3.1 and 3.3.2). The PCPA factor is reduced to 1-fold based on the rationale provided in Section 3.1.1 PCPA Hazard Consideration, resulting in a target MOE of 100. The selection of this study and target MOE is considered protective of children exposed to propoxur by the oral route.

3.2.1.4 Toxicology Endpoint Selection for Aggregate Assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential, and other non-occupational sources, and from all known or plausible exposure routes (oral and inhalation). Based on the rationale provided in Section 3.2.1.1, the non-cancer aggregate risk assessment does not require the dermal component. Acute, short-term and intermediate-term aggregate exposures to propoxur were assessed for dietary, drinking water, and residential (inhalation) exposures. The common endpoint of concern was suppressed cholinesterase activity.

For the oral component (regardless of exposure duration), the same toxicity study as for the ARfD was selected, based on an acute neurotoxicity study in which rats were dosed by gavage, with brain cholinesterase inhibition at the $BMDL_{10}$ of 0.97 mg/kg bw. Due to the lack of an appropriate acute study measuring cholinesterase inhibition by the inhalation route, this study is considered relevant for the inhalation route of exposure.

The short- and intermediate-term inhalation components of the aggregate assessment used the same 4-week rat inhalation study as outlined for the occupational and bystander risk assessment, with a NOAEL of 0.010 mg/L, or 2.6 mg/kg bw/day.

In all cases, the target MOE is 100, accounting for standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The PCPA factor is reduced to 1-fold based on the rationale provided in the PCPA Hazard Consideration section. This target MOE is considered protective of all populations, including pregnant women and their children.

3.2.1.5 Cancer Risk Assessment

For an oral cancer risk, the combined incidence rates of urinary bladder papillomas and/or carcinomas in male rats in a 106-week chronic oral toxicity study were used to generate a Q_1^* of 3.7×10^{-3} $(mg/kg\ bw/day)^{-1}$. The incidences from the main study and interim group animals were 0/57, 0/60, 1/59, 34/57 in male rats dosed at 0, 8, 42, and 222 mg/kg bw/day, respectively.

For an inhalation cancer risk, the combined incidences of hepatocellular adenomas and carcinomas were not available, thus only the incidences of hepatocellular adenomas in a chronic rat inhalation study were used to generate a Q_1^* of 4.3×10^{-2} $(mg/kg\ bw/day)^{-1}$. The incidences in male rats were 2/58, 0/60, 2/59, 6/59 at doses of 0, 0.627, 2.96, 14.4 mg/kg bw/day, respectively.

3.2.1.6 Carcinogenic Endpoint Selection for Aggregate Assessment

Aggregate exposure to propoxur was assessed for dietary, drinking water, and residential (dermal, inhalation and incidental oral) exposure. Urinary bladder papillomas and carcinomas were seen by both the oral and inhalation route in rats. In comparison, liver tumors were observed by the oral route at high dose levels in mice but not rats, as well as by the inhalation route in rats. The appropriate endpoint of concern was urinary bladder tumors because the Q_1^* value generated by the oral route for urinary bladder tumors in male rats (refer to Section 3.2.1.5) was greater than that generated for the hepatocellular adenomas in orally exposed male mice [1.9×10^{-3} $(mg/kg\ bw/day)^{-1}$ based on 10/49, 10/49, 15/49, and 21/50 incidences]. Although the Q_1^* generated for urinary bladder tumors through the inhalation route in rats [2.4×10^{-2} $(mg/kg\ bw/day)^{-1}$ based on 0/58, 0/60, 1/59, and 2/60 incidences of papillomas in males; 1.4×10^{-2} $(mg/kg\ bw/day)^{-1}$ based on 0/118, 2/117, 1/119, and 3/119 incidences of papillomas and/or carcinomas in both sexes] was greater than that via the oral route, it was attributed to the narrower dose range in the inhalation study, hence the Q_1^* from the oral route was considered more appropriate for use in the aggregate assessment in the absence of an acceptable carcinogenicity study by the dermal route, and supplemental data suggested some carcinogenic potential via this route. This cancer risk assessment is considered relevant to the dermal route of exposure. Thus the Q_1^* of 3.7×10^{-3} $(mg/kg\ bw/day)^{-1}$ for urinary bladder papillomas by the oral route in male rats is considered to be protective of all neoplasia produced by all routes of exposure.

3.2.1.7 Dermal Absorption

During the re-evaluation of propoxur, dermal absorption was evaluated to determine the most appropriate value for use in the exposure assessments for cancer risk. Two studies were considered for the evaluation of dermal absorption. These were a rat in vivo study (Eigenberg, 1988) and a human volunteer study (Feldmann and Maibach, 1974). After reviewing the available data, it was concluded that the value of 20% based on the human study is the most appropriate for use in the re-evaluation of propoxur. However, this study has several limitations including lack of a formal skin wash and collection of wash water, lack of confirmation of applied dose, lack of individual data, and no indication of completeness of urine samples. These limitations may result in an underestimate of dermal absorption.

3.2.2 Occupational Exposure and Risk Assessment

Workers can be exposed to propoxur through mixing, loading or applying the pesticide. Workers may also have postapplication exposure when entering treated sites to do routine work activities.

Uncertainty is high regarding this risk assessment because application rates for all products, and use information such as area treated per day, treatment frequency and working duration are not known. Assumptions were made based on professional judgment. It was assumed that the application rate for solutions was the same as that of the emulsifiable concentrates, that commercial applicators would use 6 aerosol cans and 20L for paintbrush application in one day, and that they would treat houses with propoxur 30 days in a year for 16 years.

Table 1 of Appendix V summarizes all use scenarios and risks of concern.

3.2.2.1 Mixer, Loader and Applicator Exposure and Risk Assessment

For commercial applicators, such as PCOs, there are potential exposures to mixers, loaders, applicators, or other handlers. Based on typical use patterns, the major scenarios identified were:

- Mixing and loading of liquids for paintbrush application
- Application of liquids by paintbrush
- Mixing, loading and applying liquids using handwand or backpack sprayers to buildings, garages, porches, screen doors, window frames, indoors, outdoors, food processing plants, commercial, industrial and institutional locations, hornet and wasp nests
- Aerosol application to boats, buses, ships, trains, bee, hornet, wasp and yellow jacket nests

Based on the toxicological profile for propoxur, a dermal non-cancer risk assessment was not required. Only inhalation exposure was assessed for the non-cancer risk assessment. Both dermal and inhalation exposures were estimated for the cancer assessment.

The number of applications per year was not provided on the label. It was assumed that workers applying propoxur would generally have a short-term intermittent exposure (up to 30 days). The following exposure scenarios were considered for commercial applicators:

a. Baseline PPE - long pants, long sleeved shirts and chemical-resistant gloves
b. Mid-Level PPE - coveralls over long pants, long sleeved shirts and chemical-resistant gloves.
c. Maximum PPE - chemical-resistant coveralls over long sleeves and long pants and chemical-resistant gloves.
d. Respirator - respirator with a NIOSH/MSHA/BHSE approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH/MSHA/BHSE approved canister approved for pesticides

Although chemical-specific handler exposure data were submitted for commercial application of propoxur, the studies were not deemed acceptable for use in the occupational risk assessment. Therefore, dermal and inhalation exposures were estimated using data from the Pesticide Handlers Exposure Database (PHED), Version 1.1. The PHED is a compilation of generic mixer/loader applicator passive dosimetry data with associated software that facilitates the generation of scenario-specific exposure estimates based on formulation type, application equipment, mix/load systems and level of PPE.

In most cases, PHED did not contain appropriate data sets to estimate exposure to workers wearing coveralls or a respirator. This was estimated by incorporating a 75% clothing protection factor for coveralls and a 90% clothing protection factor for chemical resistant coveralls into the unit exposure data.

In addition, a 90% protection factor for a respirator was incorporated into the inhalation unit exposure data. Inhalation exposures were based on light inhalation rates (17 Litres per minute [LPM] for paintbrush, aerosol, and low and high pressure handwand application equipment) and moderate inhalation rates (27 LPM) for backpack application equipment.

PHED aerosol data are representative of typical aerosol spray can applications of a pesticide with the exception of the use of the stream-type nozzle (for example, for wasp and hornet control). PHED data were generated by individuals applying a contact insecticide to the baseboards of kitchens. Hence, the exposure data in this scenario may underestimate upper body and inhalation exposure during the commercial use of stream-type nozzles, especially for application to higher cracks and crevices.

Similarly, PHED data for backpack and low pressure and high pressure handwand application is representative of treating low to mid-level shrubs generally below the waist. This scenario is not completely representative of a person using a handheld sprayer to apply pesticides to high structures. Therefore, for those exposure scenarios representing applications above the waist, the unit exposure values may underestimate exposures to the head and upper body. Thus, there is low confidence in the PHED values for these inputs.

3.2.2.2 Occupational Exposure and Non-cancer Risk Estimates

Most of the calculated inhalation MOEs are greater than the target MOE for all scenarios using baseline PPE and are not of concern. MOEs for high pressure handwand application of liquids to buildings, garages, porches, screen doors, window frames, indoors, outdoors, food processing plants, commercial, industrial and institutional locations, hornet and wasp nests reach the target MOE, provided that baseline PPE is worn during handling and a respirator is worn if handling more than 8 kg a.i. per day. Table 2 of Appendix V summarizes calculated MOEs for occupational applicators, based on currently available exposure data and the target MOE of 100.

3.2.2.3 Occupational Exposure and Cancer Risk Estimates

The cancer risk for occupational workers was determined by calculating the lifetime average daily dose (LADD) from dermal and inhalation exposure. The LADD was then compared to the Q_1^* to obtain cancer risk estimates. Occupational cancer risk is calculated assuming 16 years of exposure (i.e. a career in pesticide application of 16 years) (Carey, 1988) over a 75-year lifetime. Pesticide control operators (PCOs) were assumed to be exposed for 30 days per year. The product of the expected exposure (LADD) and the cancer potency factor (q_1^*) estimates the lifetime cancer risk as a probability. A lifetime cancer risk in the range of 1 in 10^{-5} to 1 in 10^{-6} in worker populations is generally considered acceptable.

Most of the calculated dermal and inhalation cancer risks are below the threshold of 1×10^{-5} for scenarios using baseline PPE and are not of concern. For high pressure handwand application of liquids to buildings, garages, porches, screen doors, window frames, indoors, outdoors, food processing plants, commercial, industrial and institutional locations, hornet and wasp nests, cancer risks are below the threshold and are not of concern, provided the following mitigation measures are adhered to during handling:

- Baseline PPE is worn; and
- Respirator is worn if more than 8 kg a.i. handled per day; and
- Limit to 14 kg a.i. handled per day.

Tables 3 and 4 of Appendix V summarize calculated cancer risks for occupational applicators, based on currently available exposure data.

3.2.2.4 Postapplication Worker Exposure and Risk Assessment

There is potential exposure to workers entering treated sites.

Possible occupational postapplication worker scenarios include:

Commercial applicator or pest control operator returning to treated sites for scouting; and
- workers in a treated commercial, industrial or institutional location; and
- workers in treated hotels and motels; and
- workers in treated boats, buses, ships or train; and
- workers in treated hospitals; and
- workers in treated restaurants.

A specific assessment for postapplication workers was not conducted. It was assumed that risks to postapplication workers would be similar to or less than residential postapplication risks. As cancer risks were identified for residential scenarios, there is also cancer concern for postapplication workers (refer to Section 3.2.3.3).

3.2.3 Non-Occupational Exposure and Risk Assessment

Homeowners and residents can be exposed to propoxur through applying the pesticide and when entering a treated home or handling a treated pet.

Uncertainty is high regarding this risk assessment because application rates and use information such as area treated per day, days of exposure per year, and exposure durations are not known. Assumptions were made based on survey data, professional judgment and/or using Standard Operating Procedures (SOPs). It was assumed that residential applicators would handle one container of propoxur in one day and, that they would apply propoxur 2 times per year for their entire adult life. It was also assumed that pet owners would apply 1 pet collar in one day and that they would apply pet collars 2 times a year for 38 years. The application rate used to determine postapplication exposure was calculated based on deposition data from a submitted postapplication study. It was assumed that residential applicators using propoxur in liquid, aerosol, and pet collar formulations would be exposed for 30 days per year.

3.2.3.1 Residential Applicator Exposure and Risk Assessment

There is potential exposure to homeowners applying Domestic class products containing propoxur. The following uses were assessed/considered:

- Applying liquid formulations using handheld equipment and paintbrush to residential pet quarters, spots, cracks and crevices (indoors and outdoors) and, bee, hornet, wasp and yellow jacket nests (outdoors).
- Applying aerosols to residential pet quarters, spots, cracks and crevices (indoors and outdoors) and, bee, hornet, wasp and yellow jacket nests (outdoors).
- Applying pet collars to dogs and cats
- Applying bait trays indoors.

Based on the toxicological profile for propoxur, a dermal non-cancer risk assessment was not required. Only inhalation exposure was assessed for the non-cancer risk assessment. Both dermal and inhalation exposures were estimated for the cancer assessment.

The PMRA estimated handler exposure for homeowners wearing:

- Short sleeves, short pants and no protective gloves

Applicator exposure estimates for homeowners were determined using data from PHED, studies submitted by the Outdoor Residential Exposure Task Force (ORETF) and registrant submitted studies. The PHED data is described in Section 3.2.2.1. The ORETF generated several exposure studies which monitored exposure to workers and homeowners mixing, loading, and applying pest control products to residential turf and gardens.

ORETF studies were used in the residential assessment of applicator exposure to propoxur using a hand held pump sprayer, ready-to-use pump sprayer and hand held sprayer.

ORETF also submitted a Use and Usage Survey. This survey collected residential use pattern information on application equipment, personal protective equipment, etc., used by homeowners. This use pattern information was incorporated into the applicator and postapplication risk assessments. Twenty-five percent of the ORETF Use and Usage Survey data is based on responses from Canadian households and is therefore believed to be reflective of Canadian usage. Based on the survey, 71 to 90% of users apply insecticides to structures and foundations one to two times per season.

Applicator studies were submitted by the registrant for aerosol and trigger pump spray application equipment. Exposure values from these studies were used in the risk assessment for propoxur.

The USEPA has generated standard default assumptions for developing residential exposure assessments for both handler and postapplication exposures when chemical- and/or site-specific field data are limited. These assumptions may be used in the absence of, or as a supplement to, chemical- and/or site-specific data. These assumptions generally result in high-end estimates of exposure that are protective of human health. These assumptions are outlined in the Overview of Issues Related to the SOPs and the EPA Science Advisory Council for Exposure, Policy No. 12, Recommended Revisions to the Standard Operating Procedures (SOPs) for Residential Exposure Assessments.

As per standard practice, and as proposed in the revised USEPA Residential SOPs, it was assumed that during crack and crevice application, 10% of the area would be treated. This assumption is only valid when using a nozzle tip adaptor to streamline spray (for example, straw-like device or pin stream nozzle).

There was no exposure data available to estimate exposure from handling pet collars. Exposure was estimated using the information presented in the USEPA Standard Operating Procedures (SOPs) for Residential Exposure Assessments. The assumption is that 1% of the active ingredient applied to the pet is available for dermal and inhalation exposure from handling flea collars.

Exposure from bait trays is assumed to be negligible since the active ingredient is enclosed in a plastic container and is never directly handled by the user.

3.2.3.2 Residential Applicator Exposure and Non-Cancer Risk Estimates

Homeowners can apply propoxur for indoor and outdoor residential treatment of spots and cracks and crevices, as well as stinging insect nests and pet collars for companion animals. The maximum number of applications per season is not specified on the Domestic labels. Based on survey data, it was assumed that homeowners have potential for short-term exposure to propoxur during application to residential areas (stinging insect nests, structures and foundations). Based on the USEPA Residential SOPs and/or standard practice, it was assumed that pet owners would apply 1 pet collar in one day, twice per year (also short-term exposure).

For homeowners applying propoxur to indoor and outdoor residential areas, the calculated inhalation MOEs are greater than the target MOE for all residential applicator exposure scenarios and are not of concern. Inhalation exposure from pet collars was considered to be negligible. Table 5 of Appendix V summarizes calculated inhalation MOEs for residential applicators, based on currently available exposure data and a target MOE of 100.

3.2.3.3 Residential Applicator Exposure and Cancer Risk Estimates

The cancer risk for residential applicators was determined by calculating the lifetime average daily dose (LADD) from dermal and inhalation exposure. The LADD was then compared to the Q_1^* to obtain cancer risk estimates. Residential cancer risk is calculated assuming 63 years of exposure for crack and crevice applications and 38 years of exposure for pet collar applications (i.e. pet ownership of 50 years and adult exposure is 38 of those years) over a 75-year lifetime. Residential applicators were assumed to be exposed for 2 days per year based on survey data and/or professional judgment. The product of the expected exposure (LADD) and the cancer potency factor (q_1^*) estimates the lifetime cancer risk as a probability. A lifetime cancer risk in the range of 1 in 10^{-6} in residential populations is generally considered acceptable.

The calculated dermal and inhalation cancer risks are below the residential threshold of 1×10^{-6} for all residential applicator exposure scenarios and are not of concern. Tables 6, 7 and 8 of Appendix V summarize calculated cancer risks for residential applicators, based on currently available exposure data.

3.2.3.4 Postapplication Residential Exposure and Risk Assessment

The following postapplication exposure scenarios were assessed/considered:

- Dermal exposure to adults, youth and children from propoxur residues on indoor hard and soft surfaces, following propoxur application to indoor cracks and crevices.
- Inhalation exposure to adults, youth and children from propoxur residues in air following propoxur application to indoor cracks and crevices.
- Dermal exposure to adults, youth, and children from propoxur residues on household pets following application of pet collars containing propoxur.
- Incidental oral exposure to children from propoxur residues on indoor hard and soft surfaces (i.e. surface-to-hand-to-mouth exposure) following propoxur application to indoor cracks and crevices.
- Incidental oral exposure to children from propoxur on objects that come in contact with residues (i.e. surface-to-object-to-mouth exposure) following propoxur application to indoor cracks and crevices.
- Incidental oral exposure to children from propoxur residues on the fur of companion animals wearing pet collars containing propoxur (i.e. pet-to-hand-to-mouth exposure).
- Dermal, inhalation and/or incidental oral exposure to adults, youth and children in treated commercial, industrial, and institutional locations, hotels, motels, boats, buses, ships, trains, hospitals or restaurants.

- Dermal, inhalation and/or incidental oral exposure to adults, youth and children from indoor spot and pet quarter treatments.
- Postapplication exposure to outdoor propoxur treatments.
- Postapplication exposure to indoor bait tray treatments.

Residue and dissipation data for propoxur on pet fur from pet collar use is not available. Pet collar labels state efficacy of 2-8 months. Therefore, use of 2 collars/year for both cats and dogs was assumed based on seasonal pest pressures and the label efficacy statement.

For crack and crevice treatments, indoor dissipation data for propoxur residues on hard and soft surfaces is limited. One submitted study showed no dissipation after 48 hours on treated surfaces and air. Based on survey data, it was assumed that homeowners would apply pesticides 2 times a year. Based on 2 applications per year with zero dissipation, it was assumed that there would be potential for intermediate-term exposure to individuals through contact with transferable residues following domestic and commercial application of propoxur to residential indoor cracks and crevices. The revised residential SOPs were used to generate estimates of postapplication exposure for the general public following pet collar use and crack and crevice use.

Outdoor residential crack and crevice, spot, structural and stinging insect nest treatments are limited to areas not frequented by, or inaccessible to, children and the potential for postapplication exposure is minimal. Bait tray postapplication exposure was considered to be negligible because the active ingredient is enclosed in a self-contained unit and is not available for exposure. Therefore, an assessment for bait trays and outdoor postapplication exposure was not conducted.

3.2.3.5 Postapplication Exposure and Non-Cancer Risk Estimates

Based on the toxicological profile for propoxur, a dermal non-cancer risk assessment was not required. Only inhalation exposure was assessed for the non-cancer risk assessment. Both dermal and inhalation exposures were estimated for the cancer assessment.

Postapplication inhalation exposure from pet collars was considered to be negligible based on the residential SOP.

Dermal, inhalation and/or incidental oral exposure to adults, youth and children from indoor spot and pet quarter treatments were considered to have higher exposure risks than crack and crevice application and were not assessed separately.

For crack and crevice application, the calculated inhalation MOEs are greater than the target MOE for all residential postapplication exposure scenarios and are not of concern.

For crack and crevice applications, the calculated incidental oral MOEs are greater than the target MOE for surface-to-object-to-mouth exposure and are not of concern. However, calculated MOEs for surface-to-hand-to-mouth exposure do not reach the target MOE and are risks of concern.

For pet collar applications, the calculated incidental oral MOEs for pet-to-hand-to-mouth exposure do not reach the target MOE and are risks of concern.

Tables 9 and 10 of Appendix V summarize calculated postapplication inhalation and oral MOEs for residents, based on currently available exposure data and a target MOE of 100.

3.2.3.6 Postapplication Exposure and Cancer Risk Estimates

The cancer risk for residential postapplication exposure was determined by calculating the lifetime average daily dose (LADD) from dermal, inhalation and incidental oral exposure. The LADD was then compared to the Q_1^* to obtain cancer risk estimates. Postapplication cancer risk is calculated assuming 63, 6 and 6 years of exposure for adults, youth and children respectively for crack and crevice applications and 38, 6 and 6 years of exposure for adults, youths and children respectively for pet collars (i.e. pet ownership of 50 years) over a 75-year lifetime. Residents were assumed to be exposed for 30 days per year. The product of the expected exposure (LADD) and the cancer potency factor (Q_1^*) estimates the lifetime cancer risk as a probability. A lifetime cancer risk in the range of 1 in 10^{-6} in residential populations is generally considered acceptable.

The majority of calculated oral, dermal and inhalation cancer risks are above the residential threshold of 1×10^{-6} for all residential postapplication exposure scenarios and are of concern. Incidental oral surface-to-hand-to-mouth and surface-to-object-to-mouth cancer risks are below the threshold and are not of concern.

For indoor crack and crevice applications, dermal lifetime cancer risk is above the threshold even with only 2 days of exposure per year. Inhalation lifetime cancer risk is above the threshold even with only 15 days of exposure per year. Lifetime cancer risk from the use of pet collars is above the threshold even with only 1–2 days of exposure.

Dermal, inhalation and/or incidental oral exposure to adults, youth and children from indoor spot and pet quarter treatments were considered to have higher cancer risks than crack and crevice application and were not assessed separately.

Tables 11–17 of Appendix V summarize calculated postapplication cancer risks for residents, based on currently available exposure data.

Since there are uncertainties regarding the data for crack and crevice application, data is required to support continued registration (refer to Section 8.2). In addition, to minimize potential exposures for indoor crack and crevice applications of Commercial Class products, pressurized products must be applied with a straw applicator, whereas products formulated as emulsifiable concentrates or solutions must be applied using a low pressure sprayer equipped with a pin stream nozzle to direct sprays into cracks and crevices. Also, the directions for use must be modified to provide specific instructions for crack and crevice application.

The assessment is based on the best available data. Additional data may provide a more accurate characterization of exposure.

3.3 Dietary Risk Assessment

In a dietary exposure assessment, the PMRA determines how much of a pesticide residue, including residues in milk and meat, may be ingested with the daily diet (food and drinking water). These dietary assessments are age-specific and incorporate the different eating habits of the population at various stages of life. For example, the assessments take into account differences in children's eating patterns, such as food preferences and the greater consumption of food relative to their body weight when compared to adults. Dietary risk is then determined by the combination of the exposure and the toxicity assessments. High toxicity may not indicate high risk if the exposure is low. Similarly, there may be risk from a pesticide with low toxicity if the exposure is high.

The PMRA considers limiting use of a pesticide when risk exceeds 100% of the reference dose. PMRA's Science Policy Note SPN2003-03, *Assessing Exposure from Pesticides, A User's Guide*, presents detailed acute and chronic risk assessments procedures. For cancer risk, the PMRA is concerned when the exposure estimates exceed the cancer risk unit of 1×10^{-6}.

Residue estimates used in the dietary risk assessment (DRA) may be conservatively based on the MRL or the field trial data representing the residues that may remain on food after treatment at the maximum label rate. Surveillance data representative of the national food supply may also be used to derive a more accurate estimate of residues that may remain on food when it is purchased. These include the Canadian Food Inspection Agency's (CFIA) National Chemical Residue Monitoring Program and the United States Department of Agriculture (USDA) Pesticide Data Program (PDP).

Although propoxur is not applied directly to crops, human exposure to propoxur was estimated from residues in food commodities, resulting from exposure in treated areas (for example, food handling establishments). Acute, chronic and cancer dietary exposure and risk assessments were conducted for propoxur using the Dietary Exposure Evaluation Model - Food Commodity Intake Database™ (DEEM-FCID™, Version 2.14) , which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998. The dietary risk assessment was calculated based on the highest residue detected in Domestic products (0.002 ppm) in the CFIA monitoring database (2002–2008) with the inclusion of residues detected in imported commodities, and assuming all food handling establishments in Canada use propoxur. Default processing factors were incorporated.

For more information on dietary risk estimates, residue chemistry information or monitoring data used in the dietary risk assessment for propoxur, refer to Appendices VI–IX.

3.3.1 Determination of Acute Reference Dose

To estimate acute dietary risk, the acute neurotoxicity study in the rat was selected in which significant brain cholinesterase inhibition (in both sexes) and neurological symptoms (decreased motor activity and tail-pinch responses in males, repetitive chewing in females) were observed at the LOAEL of 2 mg/kg bw.

The point of departure for the most sensitive indicator of toxicity, namely brain cholinesterase inhibition, was refined with benchmark dose modelling. The benchmark dose modelling was based on the USEPA OP Cumulative Risk Model. The reference dose was set based on the 95% lower confidence limit of the benchmark dose value at which 10% BChE inhibition was predicted to occur ($BMDL_{10}$). The $BMDL_{10}$ based on the acute neurotoxicity study is 0.97 mg/kg bw. Standard uncertainty factors used were 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The PCPA factor is reduced to 1-fold, based on the rationale provided in Section 3.1.1 PCPA Hazard Consideration. Therefore, the composite assessment factor (CAF: combined uncertainty and PCPA factors) is 100-fold.

$$\text{Acute reference dose (ARfD)} = \frac{0.97 \text{ mg/kg bw}}{100} = 0.0097 \text{ mg/kg bw}$$

The ARfD of 0.0097 mg/kg bw provides a margin of 1030 to the lowest developmental NOAEL of 10 mg/kg bw/day in the rabbit and a margin of 309 to the lowest maternal NOAEL of 3 mg/kg bw in the rat. This ARfD is thus considered protective of all populations including pregnant women and their children.

3.3.2 Acute Dietary Exposure and Risk Assessment

The acute dietary risk is calculated considering the highest ingestion of propoxur that would be likely on any one day, and using food consumption and food residue values. A statistical analysis allows all possible combinations of consumption and residue levels to estimate a distribution of the amount of propoxur residue that may be consumed in a day. A value representing the high end of this distribution is compared to the ARfD, which is the dose at which an individual could be exposed on any given day and expect no adverse health effects. When the expected intake of residues is less than the ARfD, then acute dietary exposure is not of concern.

Acute dietary (food-only) exposure to propoxur is 3.7% of the ARfD for the most exposed population of children aged 1–2 years old and is 1.6% of the ARfD for the general population; therefore it is not of concern.

3.3.3 Determination of Acceptable Daily Intake

To estimate dietary risk from repeat exposure, an acute neurotoxicity study (as discussed under Section 3.3.1) was selected for risk assessment, with the same point of departure and uncertainty factors. The $BMDL_{10}$ of 0.97 mg/kg bw is based on decreased brain cholinesterase activity in adult rats. In the case of propoxur, chronic daily exposure is considered to reflect a series of ongoing acute exposures, with each causing transient inhibition of cholinesterase. The quick acting and reversible nature of carbamates is considered as justification to default to the acute $BMDL_{10}$, which is lower than the subchronic or chronic LOAELs or NOAELs identified in dietary studies.

Similar to the ARfD, a total uncertainty factor of 100 is required to account for standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The PCPA factor can be reduced to 1-fold based on the rationale provided in Section 3.1.1 PCPA Hazard Consideration. Therefore, the CAF is 100-fold.

Acceptable Daily Intake (ADI) = 0.97 mg/kg bw = 0.0097 mg/kg bw/day
100

The ADI of 0.0097 mg/kg bw/day is considered protective of all populations including pregnant women and their children.

3.3.4 Chronic Dietary Exposure and Risk Assessment

The chronic dietary exposure is calculated using the average consumption of different foods and average residue values on those foods. This expected intake of residues is then compared to the ADI, which is the dose at which an individual could be exposed over the course of a lifetime and expect no adverse health effects. When the expected intake from residues is less than the ADI, then chronic dietary risk is not of concern.

Chronic dietary (food-only) exposure to propoxur is 2% of the ADI for the most exposed population of children aged 1-2 years old and is 0.6% of the ADI for the general population; therefore it is not of concern.

3.3.5 Determination of Cancer Potency Factor

Refer to Section 3.2.1.6 for details

3.3.6 Dietary Exposure and Cancer Risk Assessment

The lifetime cancer risk from dietary exposure is calculated by using the average consumption of different foods and the average residue values on those foods. This expected intake of residues is then multiplied by the Q_1^* to determine the cancer risk. A lifetime cancer risk that is at or below 1×10^{-6} usually does not indicate a risk concern for the general population when exposure occurs through pesticide residues in/on food and drinking water, and to otherwise unintentionally exposed person.

Based on the Q_1^* approach, the lifetime cancer risk from dietary (food-only) exposure to propoxur is 2×10^{-7} for the general population and is not of concern.

3.4 Exposure from Drinking Water

Exposure for all Canadians through drinking water is minimal. Propoxur is mainly used indoors. The few uses related to outdoor sites are close to or along perimeters of buildings. This indicates that the exposure of environmental compartments such as surface and drinking water to propoxur will be minimal. Consequently, acute, chronic and cancer exposure to propoxur through drinking water is not of concern.

3.5 Aggregate Risk Assessment (food, drinking water and residential)

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential and other non-occupational sources as well as from all known or plausible exposure routes (oral, dermal, and inhalation).

For propoxur, the relevant sources of aggregate exposure are through the diet and from residential uses. Exposure through drinking water is not expected to occur.

As risks of concern were identified for residential exposure to propoxur, an aggregate risk assessment combining residential and dietary exposures was not conducted.

Incident Reports

3.6.1 Canada

Starting April 26, 2007, registrants are required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Incidents are classified into six major categories including effects on humans, effects on domestic animals and packaging failure. Incidents are further classified by severity, in the case of humans for instance, from minor effects such as skin rash, headache, to major effects such as reproductive or developmental effects, life-threatening conditions or death.

The PMRA will examine incident reports and, where there are reasonable grounds to suggest that the health and environmental risks of the pesticide are no longer acceptable, appropriate measures will be taken, ranging from minor label changes to discontinuation of the product. Incident reports reflect the observations and opinion of the person reporting it and the Incident Reporting Program does not include validation of the reports. The PMRA collects incident reports in an effort to establish trends and the publishing of individual reports should not be considered as a statement of causality.

As of October 8, 2009 there were 1 major, 3 moderate and 4 minor human incidents reported to the PMRA for end use products containing propoxur. The majority of the reports involved Domestic class products. Four of the 8 human incident reports were formulated with propoxur alone, the rest were co-formulated with other active ingredients. Incidents of moderate severity included pain, conjunctivitis, edema, dizziness, chest congestion, nausea, and muscle weakness; whereas symptoms from the minor incidents included headaches. The major human incident resulted in hospitalization with symptoms of weakness, light-headedness, vomiting, and pneumonia and the end-use product involved in this incident was co-formulated with other active ingredients.

There were also 18 major (leading to death) and 14 minor to moderate animal incidences reported. All of the major domestic animal incident reports involved the use of pet collars and one also involved a liquid spot-on treatment. Nine of the 18 major domestic animal incident reports were formulated with propoxur alone, the rest were co-formulated with other active ingredients. Two of these major animal incidents resulted in hospitalization of the animal and the end-use products involved in these incidents were formulated with propoxur only. Symptoms for the minor to moderate incidents included drooling, ataxia, lethargy, coughing, trembling, weakness, disorientation, and vomiting. Symptoms leading to death were reportedly similar but included more severe symptoms such as dyspnea and seizures. There was also 1 package failure reported for propoxur. Causality has not been established for the effects noted in the incident reports. However, many reported symptoms are consistent with cholinergic effects.

3.6.2 USA

The USEPA reviewed the pesticide poisoning incident data for propoxur in the United States by consulting the following databases (USEPA, 1997): (1) OPP Incident Data System (1992 to April 1996) and (2) California Pesticide Illness Surveillance Program (1982-1993). More than 216 possible propoxur poisoning incidents were reported (USEPA, 1997). In most cases, symptoms for propoxur incidents were consistent with cholinergic poisoning; the exposure route was not specified but as they were either during application or postapplication, they were likely from dermal and inhalation exposure rather than oral exposure. The majority of illnesses were of a systemic type. Two exposure events from these postapplication exposures were responsible for 71 out of 91 reported incidents and resulted in symptoms including headaches, nausea, depression and respiratory irritation. In another database, 125 people exposed to propoxur reported systemic symptoms, of which 63 people reported respiratory symptoms including coughing, tightness in the chest, shortness of breath, and congestion. As a result of these incidents, USEPA required label statements to reduce exposure during and after application.

More recently, according to the California Pesticide Illness Surveillance Program (2002–2007) there were 17 human incidents from non-agricultural exposures to propoxur (none were related to agricultural use). Of these, 8 incidents were from exposure to the single chemical, propoxur and 9 incidents were from exposure to propoxur in combination with other active ingredients. Most were related to postapplication exposure. Systemic symptoms included headaches, nausea and respiratory problems. In 2009 (Updated Review of Propoxur Incident Reports, June 2009) the USEPA reported that from 2002-2009, the Office of Pesticide Programs Incident Data System reported 48 incidents in humans, a high percentage of which were from residential use of spray formulations that have since been cancelled. However, 7 occurred in humans after application of flea collars with propoxur to their pets.

Domestic animal incidents in the United States were linked in most cases to exposure from pet flea collars. Out of 49 animal incidents, fifteen dogs and nine cats were found with their flea collar "bridled" in their mouths.

4.0 Impact on the Environment

Fate and Behaviour in the Environment

Propoxur is very soluble in water. The vapour pressure indicates that propoxur is moderately volatile and Henry's law constant indicates that it is not likely to volatilize from moist soil or water.

Propoxur is stable to hydrolysis at acidic and neutral pH, but rapidly hydrolysed in alkaline pH. Photolysis may be an important route of transformation for propoxur in water (half-life of 13 d), but not in soil (half-life of 77 d).

Propoxur is moderately persistent to persistent in different soil types under aerobic conditions (DT_{50} 80–210 days), and moderately persistent under anaerobic conditions (DT_{50} 80–108 days). No data on aquatic biotransformation were available for review.

The log K_{ow} value of 1.56 for propoxur indicates that propoxur is not likely to bioaccumulate.

Propoxur is classified as highly to very highly mobile in soil adsorption/desorption studies (K_{oc} 3.4–102.6). Therefore, there is a potential for propoxur to leach to ground water and for runoff, if the use pattern included significant outdoor use. Canadian monitoring data showed no detection. However, there were detections in groundwater and surface water, as indicated by United States water monitoring data.

4.2 Risk Characterization Species

4.2.1 Risk to Terrestrial and Aquatic Organisms

Due to the use pattern, the potential exposure of aquatic and terrstrial non-target organisms is not expected to be significant. Therefore, an environmental risk assessment was not required.

5.0 Value

5.1 Commercial Class Products

5.1.1 Commercial Class Uses for Which Information on the Value of Propoxur is Sought

Appendix III lists those uses of propoxur that are not supported by the registrant. The PMRA welcomes feedback on the availability and extent of use of pesticidal alternatives to propoxur for the uses listed in Appendix III and information regarding the availability, effectiveness and extent of use of non-pesticidal pest management practices for any of the registered uses of propoxur. This information will allow the PMRA to refine sustainable pest management options for the listed site and pest combinations.

5.2 Domestic Class Products

5.2.1 Domestic Class Uses for Which Information on the Value of Propoxur is Sought

All Domestic Class uses of propoxur are listed in Appendix IIb. The PMRA has no information about the extent of use of Domestic Class products containing propoxur. The PMRA welcomes feedback on the availability and extent of use of pesticidal alternatives to these uses of propoxur as well as information regarding the availability, effectiveness and extent of use of non-chemical alternatives. This information will allow the PMRA to refine sustainable pest management options for the listed site and pest combinations.

5.3 Value of Propoxur

5.3.1 Registered alternatives to propoxur: availability, spectrum of pest control and resistance management

Propoxur has a wide spectrum of insect control. In Canada, propoxur is registered to control a wide range of insect and arthropod pests such as: ants, beetles, cockroaches, flies, fleas, millipedes, mites, mosquitoes, spiders, sow bugs, ticks, wasps, and other insect pests (excluding bed bugs) on the following sites:

- on and in structures (commercial, industrial, institutional and residential);
- in transportation vehicles such as ships, trains, trucks, etc.;
- in outdoor residential sites;
- on companion animals (cats and dogs); and
- in human habitat and recreational sites to control black flies and mosquitoes.

Propoxur's broad spectrum of control of insects and arthropods makes it valuable as an alternative active ingredient to the synthetic pyrethroids (MoA group 3 insecticides), which are also registered for the control of a wide range of structural pests and account for the majority of products registered in Canada for this use. Other alternative active ingredients to propoxur (excluding fumigants) that are registered for use in Canada with a broad spectrum of control for structural pests include silicon dioxide (diatomaceous earth and silica aerogel) and boric acid. Additional alternative active ingredients registered for the control of structural pests include abamectin (MoA group 6), hydramethylnon (MoA group 20), imidacloprid (MoA group 4) and German cockroach extract. Abamectin and hydramethylnon are registered for the control of ants and cockroaches only, while imidacloprid and German cockroach extract are registered for the control of cockroaches only.

In recent years, the structural uses of several carbamate and organophosphate insecticides (MoA group 1A and 1B insecticides, respectively) have been discontinued or their registered use patterns have been amended (see Table 5.3.1). The discontinuation of carbamate and organophosphate active ingredients, or amendment to their registered uses, limits the availability and viability of alternative active ingredients from MoA groups 1A and 1B for rotation with the synthetic pyrethroids.

Alternative active ingredients to propoxur are available in Canada for the control of fleas and ticks on cats and dogs. These include active ingredients formulated into pet collars and shampoos. Veterinary drugs are also available for control of fleas and ticks on dogs and fleas on cats.

Alternative active ingredients to propoxur are available in Canada for the control of mosquitoes. Mosquito control includes the use of larvicidal pesticides such as s-methoprene, chlorpyrifos, *Bacillus thuiringiensis* var. *israelensis* and *Bacillus sphaericus* and mosquito adulticides such as permethrin, d-trans allethrin, chlorpyrifos, dichlorvos, malathion and naled (for use in agricultural areas only). As published in REV2003-03 *Re-evaluation of Malathion: Assessment of Use in Mosquito Abatement Programs*, the PMRA has determined that large-scale applications of malathion in residential areas for control of adult mosquitoes do not pose an unacceptable risk to bystanders and operators (mixer/loaders and applicators) when used in accordance with the recommended label amendments.

Table 5.3.1 Use pattern amendments to carbamates and organophosphates (MoA group 1A and 1B insecticides, respectively) used to control structural pests.

Active ingredient	Comments
Bendiocarb (group 1A)	**REV2002-06 *Re-evaluation of selected Carbamate Pesticides*, identified bendiocarb as an active ingredient that is subject to re-evaluation. Products formulated with bendiocarb have been voluntarily discontinued by registrants. As of November 18, 2009, only one product, Ficam D 1% Dust Insecticide (Reg. No. 16080) is registered for use in Canada. Registration of this product will expire on December 31, 2013 after which this product may no longer be used.**
Chlorpyrifos (group 1B)	**As stated in REV2000-05 *Chlorpyrifos* and implemented in REV2007-01 *Update on the Re-evaluation of Chlorpyrifos* the chlorpyrifos labels have been revised for non agricultural uses as follows:** **○ All residential uses (indoor and outdoor) have been phased out with the exception of bait traps to control ants.** **○ Uses inside and outside commercial buildings, where public access is limited have been limited to:** **• Indoors: spot treatment, crack and crevice applications and bait treatments;** **• Outdoors: perimeter soil treatment or localized areas on outside surfaces of industrial plants, manufacturing plants, warehouses, meat packing plants and food processing plants.** **○ As of November 18, 2009, chlorpyrifos is registered for use in farm and livestock buildings (indoors and outdoors) for the control of flies and certain other insect pests.** **○ Public health uses, notably mosquito control, that are currently on the registered labels as of November 18, 2009 are currently under re-evaluation.**

Active ingredient	Comments
	For additional information please consult REV2007-01.
Diazinon (group 1B)	**REV2000-07 and REV2000-08 both titled *Update on the Re-evaluation of Diazinon in Canada* stated that registrants of diazinon products voluntarily discontinued the residential indoor diazinon uses (including pet collars). Phase out began in 2001 with provisions to carry over remaining product until 2003 when registration expired. As indicated in REV2005-06 *Preliminary Risk and Value Assessment of Diazinon*, the non-residential structural uses of diazinon were not supported by the registrants and were voluntarily discontinued. In addition, as published in PRVD2007-16 *Diazinon*, and in RVD2009-18 *Diazinon,* the remaining uses of diazinon are to be phased out.**
Dichlorvos (group 1B)	**Dichlorvos is currently under re-evaluation. As published in REV2008-04 *Dichlorvos Interim Measures,* application of dichlorvos as a crack and crevice treatment and application by hand held fogger will be discontinued for all uses. Additionally, use of dichlorvos in some structural sites (wine cellars and dog kennels) will be discontinued. Application of dichlorvos using automated foggers for structural sites such as food processing plants, industrial plants, warehouses, stables and barns is still included on the registered labels as of November 18, 2009.**
Malathion (group 1B)	**REV99-01 Re-*evaluation of Organophosphate Pesticides*, states that malathion (including the structural uses such as food processing plants, flour and feed mills, bakeries etc.) is currently under re-evaluation.**
Propetamphos (group 1B)	**Mitigation measures implemented as a result of re-evaluation of propetamphos as published in REV2003-01 *Re-evaluation of Propetamphos*, include:** **o removing propetamphos use in residential and institutional structures (except food service areas);** **o limitation to use as a crack and crevice treatment; and** **o removal of pests controlled by spot treatment.**

5.3.2 Rapid knockdown and long residual action.

Knockdown, which is characterized as an insect's inability to walk or fly, is rapid with propoxur. Residual action allows propoxur to continue to kill insect pests even after the spray has dried. This is important for the control of public health pests such as mosquitoes and cockroaches where immediate and prolonged reduction of a pest population is required. Propoxur is typically used when control with alternative products has failed.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances (those that meet all four criteria outlined in the policy, i.e. persistent (in air, soil, water and /or sediment, bioaccumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*).

During the review process, propoxur and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[6] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

Propoxur does not meet Track 1 criteria, and is not considered a Track 1 substance. See Table 3 (Appendix X) for comparison with Track 1 criteria.

Propoxur does not form any transformation products that meet all Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette.*[7] The list is used as described in the PMRA Notice of Intent NOI2005-01[8] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02,[9] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

Technical grade propoxur and the end-use products do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette.*

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6 DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy.*

7 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

8 NOI2005-01, List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.

9 DIR2006-02, PMRA Formulants Policy.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for propoxur is adequate to define the majority of toxic effects that may result from human exposure to propoxur. In subchronic and chronic studies on laboratory animals, the primary effects were cholinesterase inhibition (resulting in neurotoxic clinical signs such as tremors, but not neuropathy) and liver toxicity. Propoxur was not mutagenic but may cause chromosome aberrations. There was evidence of urinary bladder carcinogenicity in rats and mice by long-term oral or inhalation exposure. Liver carcinogenicity in male mice by the oral route and male rats by the inhalation route was also noted. There was no evidence of increased susceptibility of the young in reproduction or developmental toxicity studies. In reproductive studies, maternal cholinesterase activity was the most sensitive endpoint, although cholinesterase inhibition was not measured in offspring. Propoxur was not teratogenic in developmental studies. In supplementary studies, propoxur was an immunosuppressant. Only uses for which exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

7.1.1 Occupational Risk

Non-cancer and cancer risk estimates associated with mixing, loading and applying activities for labeled uses are not of concern for all Commercial class uses, provided personal protective equipment are used and restrictions are made to the amount of active ingredient handled per day.

7.1.2 Non-Occupational Risk or Residential Risk

Non-cancer and cancer risk estimates associated with application activities for current labeled uses are not of concern for all residential uses. The majority of indoor postapplication non-cancer risks associated with residential exposure for labeled uses are not of concern. For children, indoor incidental oral exposure from surface-to-hand-to-mouth and pet-to-hand-to-mouth transfer is of concern. The majority of indoor postapplication cancer risks associated with residential exposure for labeled uses are of concern. To minimize potential exposures for indoor applications, discontinuation of indoor uses of Domestic class products (except for bait trays) is proposed. In addition, Commercial class products formulated as emulsifiable concentrates or solutions must be applied using a low pressure sprayer equipped with a pin stream nozzle and pressurized products must be equipped with a straw applicator to direct spray into cracks and crevices. Also, the directions for use must be modified to provide specific instructions for crack and crevice application only. Any further mitigation for both crack and crevice uses and pet collars uses are not feasible.

Outdoor residential crack and crevice, spot, structural and stinging insect nest treatments are limited to areas not frequented by, or which are inaccessible to children. Therefore, the potential for postapplication exposure is minimal. Bait tray applicator and postapplication exposure was considered to be negligible because the active ingredient is enclosed in a self-contained unit and is not available for exposure. Therefore, there are no risks of concern for bait tray and outdoor postapplication exposure.

Uncertainty is high in this risk assessment because application rates, adequate transferable residue data and dissipation data were not provided by the registrant. The risk assessment may be refined with more use information.

7.1.3 Dietary Risk from Food

Acute, chronic and lifetime cancer dietary risks from food-only exposure to propoxur are not of concern.

7.1.4 Dietary Risk from Drinking Water

Risk assessment of exposure from drinking water was not conducted as exposure for all Canadians through drinking water is minimal.

7.1.5 Aggregate Risk

As there were residential risks of concern, an aggregate risk assessment was not conducted.

7.2 Environmental Risk

Due to the current use pattern, environmental exposure is expected to be limited and, therefore, a risk assessment was not required.

7.3 Value

Propoxur is a non-systemic carbamate insecticide used to control a broad range of insect pests on a wide variety of sites including structures (indoors and outdoors), transportation vehicles, on companion animals, in human habitat and recreational areas (for biting fly and mosquito control) and in residential outdoor areas.

Propoxur is important in the resistance management of structural insect and arthropod pests as it provides an option for rotation with insecticides from other chemical groups, especially the synthetic pyrethroids which account for the majority of products registered in Canada for this use. Excluding fumigants, boric acid and silicon dioxide (diatomaceous earth and silica aerogel) are the only alternative active ingredients to propoxur with a broad spectrum of pest control that are available for rotation with the synthetic pyrethroids. Alternative active ingredients are available for mosquito control and the pet collar uses of propoxur.

Propoxur is characterized as providing rapid knock down and has a long residual action. This is important for the control of public health pests such as mosquitoes and cockroaches where immediate and prolonged reduction of a pest population is required.

8.0 Proposed Regulatory Decision

After a re-evaluation of propoxur, Health Canada's Pest Management Regulatory Agency, under the authority of the *Pest Control Products Act*, is proposing continued registration of some propoxur uses in Canada, provided that the mitigation measures described in this document are implemented and required data is submitted. These uses include indoor crack and crevice applications of Commercial class products and outdoor uses of Domestic and Commercial class products, as well as bait trays.

Certain uses of propoxur are proposed for phase-out as registrants do not support continued registration or because of the human health risks. These are: use to control biting flies including mosquitoes, black flies, sandflies and punkies, pet collar use, and all indoor uses on Domestic class products, except bait trays.

Proposed mitigation measures and use limitations are presented in Appendix XII, and data requirements are presented in Section 8.2.

8.1 Proposed Regulatory Actions

8.1.1 Proposed Regulatory Action Related to Human Health

Based on the evaluation of available scientific information, the health risks associated with propoxur, under the current conditions of use are of concern. Therefore, additional data is requested to refine the risk assessment and mitigation measures are proposed. Notwithstanding uncertainties in the risk assessment, there is a high level of concern for pet collar products containing propoxur as well as all indoor uses of Domestic class propoxur products (except bait trays). Consequently, all pet collar and indoor uses of Domestic class products containing propoxur (excluding bait trays) are proposed for phase out.

8.1.1.1 Occupational Exposure

Proposed Mitigation for Mixer, Loader and Applicator Exposure

Baseline personal protective equipment are required for all uses; a respirator is required for handheld equipment if more than 8 kg active ingredient is handled per day with a maximum limit of 14 kg active ingredient handled per day.

8.1.1.2 Residential Exposure

Proposed Mitigation for Postapplication Exposure

All pet collar and indoor uses of Domestic class products containing propoxur (excluding bait trays) are proposed for phase out.

To minimize potential exposures for indoor crack and crevice applications of Commercial Class products, pressurized products must be applied with a straw applicator, whereas products formulated as emulsifiable concentrates or solutions must be applied using a low pressure sprayer equipped with a pin stream nozzle to direct sprays into cracks and crevices. Also, the directions for use must be modified to provide specific instructions for crack and crevice application. Further data are required to refine the risk assessment.

8.1.1.3 Residue Definition for Risk Assessment and Enforcement

The residue definition has not been established in Canada for propoxur. However, metabolism studies indicate propoxur is rapidly absorbed and metabolized following ingestion. The residue of concern in animals and plants is defined as the parent compound by the U.S. and the Joint FAO/WHO Meetings on Pesticide Residues (JMPR). It is proposed that the residue in Canada be defined as the parent compound, propoxur.

8.1.1.4 Maximum Residue Limits for Propoxur in Food

In general, when the re-evaluation of a pesticide has been completed, the PMRA intends to update Canadian MRLs and to remove MRLs that are no longer supported. The PMRA recognizes, however, that interested parties may want to retain an MRL in the absence of a Canadian registration to allow legal importation of treated commodities into Canada. The PMRA requires similar chemistry and toxicology data for such import MRLs as those required to support Canadian food use registrations. In addition, the PMRA requires residue data that are representative of use conditions in exporting countries, in the same manner that representative residue data are required to support domestic use of the pesticide. These requirements are necessary so that the PMRA may determine whether the requested MRLs are needed and to ensure they would not result in health risk concerns.

MRLs for pesticides in or on food are established by Health Canada's PMRA under authority of the *Pest Control Products Act*. After the revocation of an MRL or where no specific MRL for a pest control product has been established, subsection B.15.002(1) of the Food and Drug Regulations applies. This requires that residues do not exceed 0.1 ppm and has been considered a general MRL for enforcement purposes. However, changes to this general MRL may be implemented in the future, as indicated in Information Note: Progress on Minimizing Reliance on the 0.1 Parts per Million as a General Maximum Residue Limit for Food Pesticide Residue, December 2009.

No Canadian MRLs have been established for propoxur residues in/on any commodity.

A complete list of MRLs established in Canada can be found on the PMRA's MRL web page (http://www.hc-sc.gc.ca/cps-spc/pest/protect-proteger/food-nourriture/mrl-lmr-eng.php).

8.1.2 Proposed Regulatory Action Related to Environment

Environmental mitigative measures are not needed due to minimal environmental exposure and thus negligible risk to non-target organisms.

8.1.3 Proposed Regulatory Action Related to Value

There are no regulatory actions based upon value proposed at this time for the continued registration of propoxur.

Additional Data Requirements

The following studies are required under section 12 of the *Pest Control Products Act*:

Data Requirements Related to Toxicology

DACO 4.5.12 There was no sensitivity of the young demonstrated in the database, but an acute comparative cholinesterase study (i.e., juvenile versus adult animals) in rats is required due to the neurotoxic potential of propoxur to adults.

Data Requirements Related to Residential Exposure Assessment (Section 12)

DACO 5.2 Commercial Crack and Crevice Application

- Application rates in g a.i/cm2 for all Commercial class products
- Area treated per day (ATPD) for commercial application using paintbrush and aerosols.
- Treatment frequency (i.e. number of days of exposure per year) for commercial applicators.
- Working duration for pesticide control operators.
- Number of days of exposure per year for residents.

DACO 5.9 Indoor transferable residue and dissipation data following crack and crevice application in residential scenarios based on the Canadian use pattern (for example, application rates). This study methodology needs to be consistent with the transfer coefficient in the USEPA Residential SOPs.

DACO 5.10 Indoor air monitoring data and dissipation data following crack and crevice application in residential areas based on the Canadian use pattern (for example, application rates).

The following studies may refine the risk assessment but are not required under section 12 of the *Pest Control Products Act*.

DACO 5.6/5.7 Postapplication Residential - passive dosimetry or biological monitoring for Domestic products.

List of Abbreviations

a.i.	active ingredient
ADD	absorbed daily dose
ADI	Acceptable Daily Intake
ARfD	Acute Reference Dose
ATPD	area treated per day
BChE	brain cholinesterase activity
BHSE	British Health and Safety Executive
BMDL10	lower confidence limit on the benchmark dose associated with a 10% response
bw	body weight
BWG	body weight gain
CAF	Composite Assessment Factor
Cal/EPA	California Environmental Protection Agency
CAS	Chemical Abstracts Service
CFIA	Canadian Food Inspection Agency
cm2	centimetres squared
CSFII	Continuing Surveys of Food Intakes by Individuals
DA	dermal absorption
DACO	Data Coding
DEEM	Dietary Exposure Evaluation Model
EC	emulsifiable concentrate
EChE	erythrocyte cholinesterase activity
EFSA	European Food Safety Authority
et al	and others
EU	European Union
FCID	Food Commodity Intake Database
FDA	United States Food and Drug Administration
g	gram(s)
g a.i.	grams of active ingredient
GI	gastrointestinal
GLC	Gas Liquid Chromatography
GLC-ECD	Gas Liquid Chromatography - Electron Capture Detection
HP	high pressure
hr/hrs	hour(s)
i.e.	specifically
JMPR	Joint FAO/WHO Meetings on Pesticide Residues
kg	kilogram(s)
L	litre(s)
LADD	lifetime average daily dose
LC50	lethal concentration to 50%
LCI	Lower Confidence Interval
LD50	lethal dose to 50%
LOAEL	lowest observed adverse effect level
LOD	Limit of Detection
LODRES	Value of ½ Limit of Detection
LOEL	lowest observed effect level
LOQ	Limit Of Quantitation

LP	low pressure
LPM	litres per minute
m^3	metre(s) cubed
mg	milligram(s)
mm	millimetre(s)
MOE	margin of exposure
MRID	Master Record Identifier for the USEPA
MRL	Maximum Residue Limit
MRM	Multi-Residue Analytical Methodology
MSHA	Mines, Safety, Health Association
N/A	Not Applicable
NIOSH	National Institute for Occupational Safety and Health
No.	number
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NRDC	Natural Resources Defense Council
ORETF	outdoor residential exposure task force database
PAM	Pesticide Analytical Manual
PChE	plasma cholinesterase activity
PCO	pesticide control operator
PCPA	*Pest Control Products Act*
PDP	Pesticide Data Program
PHED	pesticide handlers exposure database
PMRA	Pest Management Regulatory Agency
PP	pressurized product
ppb	parts per billion
PPE	personal protective equipment
ppm	parts per million
PRVD	Proposed Re-evaluation Decision
Q_1^*	cancer potency factor
RED	Reregistration Eligibility Decision
RUAS	Re-evaluation and Use Analysis Section
SN	solution
SOP	standard operating procedures
SR	slow release
TGAI	technical grade active ingredient
TR	transferable residues
UCI	Upper Confidence Interval
USDA	United State Department of Agriculture
USEPA	Unites States Environmental Protection Agency
µg	microgram(s)

Appendix I Propoxur products registered in Canada excluding discontinued products or products with a submission for discontinuation as of January 28, 2009, based upon the PMRA's Electronic Pesticide Regulatory System (e-PRS) database.

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee
18277	Technical Grade Active Ingredient	MCLAUGHLIN GORMLEY KING COMPANY	PROPOXUR TECHNICAL INSECTICIDE	Solid	Propoxur 96%
23906	Manufacturing Concentrate	MCLAUGHLIN GORMLEY KING COMPANY	PYROCIDE INTERMEDIATE 7045	Solution	Propoxur 5.89%; Pyrethrins 0.59%; Piperonyl butoxide 1.18%; N-octyl bicycloheptene dicarboximide 1.97%
10233	Commercial	MCLAUGHLIN GORMLEY KING COMPANY	PROPOXUR LIQUID CONCENTRATE INSECTICIDE	Emulsifiable concentrate	Propoxur 180 g/L
11565	Commercial	GARDEX CHEMICALS LTD.	GARDEX 1% BAYGON RESIDUAL INSECTICIDE	Solution	Propoxur 1%
15565	Commercial	AGRIUM ADVANCED TECHNOLOGIES RP INC.	PRO PROX-120 ULV INSECTICIDE CONCENTRATE	Solution	Propoxur 120 g/L
20015	Commercial	MCLAUGHLIN GORMLEY KING COMPANY	HORNET & WASP KILLER II	Pressurized product	Propoxur 0.500%; N-octyl bicycloheptene dicarboximide 0.167%; Pyrethrins 0.05%; Piperonyl butoxide 0.100%
22122	Commercial	MEGA-LAB MANUFACTURING CO. LTD.	BUZZ-OFF WASP & HORNET BLASTER	Pressurized product	Propoxur 0.50%; Pyrethrins 0.05%; Piperonyl butoxide 0.100%; N-octyl bicycloheptene dicarboximide 0.166%
22661	Commercial	CHEMICAL PACKAGING CORP.	TERAND WASP & HORNET KILLER	Pressurized product	Propoxur 0.50%; Pyrethrins 0.05%; Piperonyl butoxide 0.100%; N-octyl bicycloheptene dicarboximide 0.166%
24082	Commercial	K-G PACKAGING INC	K-G INSECTICIDE III	Pressurized product	Propoxur 2%; Piperonyl butoxide 8%

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee
24190	Commercial	AGRIUM ADVANCED TECHNOLOGIES RP INC.	PRO BUG-X RESIDUAL HOUSEHOLD INSECT SPRAY	Solution	Propoxur 1%
24398	Commercial	K-G PACKAGING INC	K-G INSECTICIDE IV	Pressurized product	Propoxur 1%
24858	Commercial	AIR GUARD CONTROL (CANADA) LIMITED	KONK 400 RESIDUAL INSECTICIDE SPRAY WITH BAYGON	Pressurized product	Propoxur 2%; Piperonyl butoxide 8%
28658	Commercial	BETTER THAN CORPORATION	TKO MAXX PRO CRACK, CREVICE & SURFACE RESIDUAL INSECTICIDE FOR RESIDENTIAL, INDUSTRIAL, COMMERCIAL & FOOD PROCESSING/HANDLING PESTS	Pressurized product	Propoxur 2%; Piperonyl butoxide 8%
14873	Domestic	AGRIUM ADVANCED TECHNOLOGIES RP INC.	PRO B1 HOME & APARTMENT INSECTICIDE	Solution	Propoxur 1%
14877	Domestic	AGRIUM ADVANCED TECHNOLOGIES RP INC.	WILSON BUG-X READY-TO-USE RESIDUAL HOUSEHOLD INSECT SPRAY	Solution	Propoxur 1%
17201	Domestic	SURE-GRO IP INC.	WILSON MOSQUITO FOGGING INSECTICIDE	Solution	Propoxur 0.5%
17922	Domestic	K-G PACKAGING INC	K-G HORNET & WASP KILLER	Pressurized product	Propoxur 0.5%
17926	Domestic	K-G PACKAGING INC	K-G ANT & ROACH KILLER	Pressurized product	Propoxur 0.5%
18494	Domestic	SUREKILLER PRODUCTS LTD.	INSTANT PRESSURIZED RESIDUAL INSECTICIDE SPRAY	Pressurized product	Propoxur 0.5%
18505	Domestic	WELLMARK INTERNATIONAL	VET-KEM INTEGRAL BUCKLE FLEA & TICK COLLAR FOR DOGS	Slow release generator	Propoxur 9.4%
18506	Domestic	WELLMARK INTERNATIONAL	VET KEM BREAKAWAY FLEA & TICK COLLAR FOR CATS	Slow release generator	Propoxur 9.4%
19210	Domestic	WELLMARK INTERNATIONAL	ZODIAC BREAKAWAY FLEA & TICK COLLAR FOR CATS	Slow release generator	Propoxur 9.4%
19211	Domestic	WELLMARK INTERNATIONAL	ZODIAC FLEA & TICK COLLAR FOR DOGS WITH INTEGRAL BUCKLE	Slow release generator	Propoxur 9.4%
19596	Domestic	K-G PACKAGING INC	K-G HORNET & WASP KILLER IIB	Pressurized product	Propoxur 0.50%; Pyrethrins 0.05%; Piperonyl butoxide 0.100%; N-octyl bicycloheptene dicarboximide 0.166%

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee
19598	Domestic	K-G PACKAGING INC	K-G CRAWLING INSECT KILLER IIB	Pressurized product	Propoxur 0.50%; Pyrethrins 0.05%; Piperonyl butoxide 0.100%; N-octyl bicycloheptene dicarboximide 0.166%
19831	Domestic	ALBERTA AEROSOL-GILLEX	ROACH & ANT KILLER WITH BAYGON	Pressurized product	Propoxur 1.5%
20016	Domestic	MCLAUGHLIN GORMLEY KING COMPANY	HORNET & WASP KILLER IIB	Pressurized product	Propoxur 0.50%; Pyrethrins 0.05%; Piperonyl butoxide 0.100%; N-octyl bicycloheptene dicarboximide 0.167%
20021	Domestic	MCLAUGHLIN GORMLEY KING COMPANY	CRAWLING INSECT KILLER IIB	Pressurized product	Propoxur 0.50%; Pyrethrins 0.05%; Piperonyl butoxide 0.100%; N-octyl bicycloheptene dicarboximide 0.167%
20096	Domestic	K-G PACKAGING INC	K-G HORNET & WASP KILLER IIIB	Pressurized product	Propoxur 0.50%; Pyrethrins 0.05%; Piperonyl butoxide 0.100%; N-octyl bicycloheptene dicarboximide 0.166%
20471	Domestic	PIC CORP.	PIC ROACH CONTROL SYSTEM	Paste	Propoxur 2%
20737	Domestic	ALBERTA AEROSOL-GILLEX	BUGCON DUAL ACTION	Pressurized product	Propoxur 0.50%; Pyrethrins 0.05%; Piperonyl butoxide 0.100%; N-octyl bicycloheptene dicarboximide 0.166%
20742	Domestic	ALBERTA AEROSOL-GILLEX	BUGCON TOTAL EXTERMINATOR	Solution	Propoxur 1.5%
23299	Domestic	SPRAY-PAK INDUSTRIES INC.	SPRAY PAK WASP & HORNET KILLER II	Pressurized product	Propoxur 0.50%; Pyrethrins 0.05%; Piperonyl butoxide 0.100%; N-octyl bicycloheptene dicarboximide 0.166%

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee
23299.02	Domestic	CAN-VET ANIMAL HEALTH SUPPLIES LTD	BUGWACKER WASP & HORNET KILLER	Pressurized product	Propoxur 0.50%; Pyrethrins 0.05%; Piperonyl butoxide 0.100%; N-octyl bicycloheptene dicarboximide 0.166%
23831	Domestic	ALBERTA AEROSOL-GILLEX	POULIN'S SUPER STRENGTH RESIDUAL INSECTICIDE	Solution	Propoxur 1.5%
23832	Domestic	ALBERTA AEROSOL-GILLEX	MEGA TOTAL EXTERMINATOR INSECTICIDE SOLUTIONS	Solution	Propoxur 1.5%
23968	Domestic	HOME HARDWARE STORES LTD.	HOME GARDENER WASP & HORNET KILLER	Pressurized product	Propoxur 0.5%
23969	Domestic	HOME HARDWARE STORES LTD.	HOME GARDENER CRAWLING INSECT KILLER	Pressurized product	Propoxur 0.5%
24086	Domestic	ALBERTA AEROSOL-GILLEX	COMBAT PLUS RESIDUAL INSECTICIDE SOLUTION	Solution	Propoxur 1.5%
24237	Domestic	ALBERTA AEROSOL-GILLEX	S.D. HEAVYDUTY BUG KILLER	Solution	Propoxur 1.5%
24634	Domestic	LLOYDS LABORATORIES	LLOYDS HORNET & WASP BLASTER	Pressurized product	Propoxur 0.50%; Pyrethrins 0.05%; Piperonyl butoxide 0.100%; N-octyl bicycloheptene dicarboximide 0.166%
24699	Domestic	LES PRODUITS DE CONTROLE SUPERIEUR INC/ SUPERIOR CONTROL PRODUCTS INC	SUPER HUNTER OF MOSQUITOES & BLACKFLIES	Solution	Propoxur 0.5%
24838	Domestic	AGRIUM ADVANCED TECHNOLOGIES RP INC.	PRO ATACK HORNET & WASP KILLER	Pressurized product	Propoxur 0.50%; Pyrethrins 0.05%; Piperonyl butoxide 0.100%; N-octyl bicycloheptene dicarboximide 0.167%
26506	Domestic	CAMCO	SUPER KILL II ROACH & ANT KILLER	Pressurized product	Propoxur 0.50%; Pyrethrins 0.05%; Piperonyl butoxide 0.100%; N-octyl bicycloheptene dicarboximide 0.167%

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee
26960	Domestic	NPI BUGCON	BEDESSEE'S ROACH AND ANT KILLER	Pressurized product	Propoxur 1.5%
27086	Domestic	NPI BUGCON	BUGCON ZEP WASP & HORNET KILLER	Pressurized product	Propoxur 0.50%; Pyrethrins 0.05%; Piperonyl butoxide 0.100%; N-octyl bicycloheptene dicarboximide 0.166%
27427	Domestic	THE JOHN LIM CO. LTD.	SUPER K RESIDUAL INSECT SPRAY	Solution	Propoxur 1%
27508	Domestic	NPI BUGCON	MEGA WASP & HORNET KILLER - FLEA & TICK KILLER CRAWLING INSECT KILLER	Pressurized product	Propoxur 0.50%; Pyrethrins 0.05%; Piperonyl butoxide 0.100%; N-octyl bicycloheptene dicarboximide 0.166%
27546	Domestic	EMU POLISHES INC.	SPIKE HORNET AND WASP KILLER	Pressurized product	Propoxur 0.50%; Pyrethrins 0.05%; Piperonyl butoxide 0.100%; N-octyl bicycloheptene dicarboximide 0.167%
27549	Domestic	EMU POLISHES INC.	SPIKE CRAWLING INSECT KILLER	Pressurized product	Propoxur 0.50%; Pyrethrins 0.05%; Piperonyl butoxide 0.100%; N-octyl bicycloheptene dicarboximide 0.167%
27607	Domestic	ROLF C. HAGEN INC.	HAGEN FLEA COLLAR FOR DOGS & PUPPIES WITH INTEGRAL BUCKLE	Slow release generator	Propoxur 9.48%
27608	Domestic	ROLF C. HAGEN INC.	HAGEN FLEA COLLAR FOR MEDIUM DOGS WITH INTEGRAL BUCKLE	Slow release generator	Propoxur 9.48%
27609	Domestic	ROLF C. HAGEN INC.	HAGEN FLEA COLLAR FOR PUPPIES & SMALL DOGS WITH INTEGRAL BUCKLE	Slow release generator	Propoxur 9.48%
27610	Domestic	ROLF C. HAGEN INC.	HAGEN FLEA COLLAR FOR LARGE DOGS WITH INTEGRAL BUCKLE	Slow release generator	Propoxur 9.48%
27611	Domestic	ROLF C. HAGEN INC.	HAGEN FLEA COLLAR FOR CATS & KITTENS WITH INTEGRAL BUCKLE	Slow release generator	Propoxur 9.48%

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee
27612	Domestic	ROLF C. HAGEN INC.	HAGEN FLEA CONTROL COLLAR FOR CATS AND KITTENS WITH INTEGRAL BUCKLE	Slow release generator	Propoxur 9.48%
27667	Domestic	ROLF C. HAGEN INC.	SERGEANT'S FLEA COLLAR FOR CATS AND KITTENS WITH INTEGRAL BUCKLE	Slow release generator	Propoxur 9.48%
27668	Domestic	ROLF C. HAGEN INC.	SERGEANT'S FLEA COLLAR FOR SMALL DOGS AND PUPPIES WITH INTEGRAL BUCKLE	Slow release generator	Propoxur 9.48%
27669	Domestic	ROLF C. HAGEN INC.	SERGEANT'S FLEA COLLAR FOR MEDIUM DOGS WITH INTEGRAL BUCKLE	Slow release generator	Propoxur 9.48%
27670	Domestic	ROLF C. HAGEN INC.	SERGEANT'S FLEA COLLAR FOR LARGE DOGS WITH INTERGRAL BUCKLE	Slow release generator	Propoxur 9.48%
27710	Domestic	SUREKILLER PRODUCTS LTD.	SUREKILLER CRAWLING INSECT KILLER II	Pressurized product	Propoxur 0.50%; Pyrethrins 0.05%; Piperonyl butoxide 0.100%; N-octyl bicycloheptene dicarboximide 0.166%
28121	Domestic	THE FOUNTAINHEAD GROUP INC.	BLACK FLAG FOG INSECTICIDE	Solution	Propoxur 0.5%
28199	Domestic	WELLMARK INTERNATIONAL	ZODIAC POWERBAND PLUS DUAL ACTION FLEA & TICK COLLAR FOR CATS & KITTENS	Slow release generator	Propoxur 10%; s-methoprene 2.10%
28360	Domestic	WELLMARK INTERNATIONAL	ZODIAC POWERBAND PLUS DUAL ACTION FLEA & TICK COLLAR FOR DOGS & PUPPIES	Slow release generator	Propoxur 10%; s-methoprene 2.10%
28598	Domestic	WELLMARK INTERNATIONAL	VET KEM(R) OVITROL(R) DUAL ACTION COLLAR FOR CATS & KITTENS	Slow release generator	Propoxur 10%; s-methoprene 2.10%
28599	Domestic	WELLMARK INTERNATIONAL	VET KEM(R) OVITROL(R) DUAL ACTION COLLAR FOR DOGS & PUPPIES	Slow release generator	Propoxur 10%; s-methoprene 2.10%

Appendix IIa Commercial Class uses of propoxur registered in Canada, excluding uses of discontinued products or products with a submission for discontinuation as of December 22, 2008.

Site(s)	Pest(s)	Formulation Type	Application Methods and Equipment	Application Rate (g a.i.)		Maximum Number of Applications per Year	Minimum Number of Days Between Applications	Registrant Supports the Use?
				Maximum Single	Maximum Cumulative			
Use Site Category # 20: Structural; and/ or Use Site Category # 33: Residential Outdoors								
Indoors (excluding: food, feed, drink, dishes, utensils, food storage areas, and food preparation surfaces)	Ants, cockroaches, earwigs, fleas, millipedes, saw-toothed grain beetle (exposed stages), ticks	Emulsifiable concentrate	Surface spot spray, crack and crevice spray: hand held sprayers	11.7 g/L	Not stated	Not stated	Not stated	Yes
	Ants, brown dog tick, cockroaches, crickets, saw-toothed grain beetle (exposed stage), silverfish, spiders	Solution		Not stated	Not stated			
Commercial locations, industrial locations, institutional locations	Ants, brown dog tick, cockroaches, clover mite, crickets, earwigs, fleas, flies, gnats, millipedes, scorpions, silverfish, sowbugs, spiders Exposed Stages of: Angoumois grain moth, cigarette beetle, drugstore beetle, Indian meal moth, saw-toothed grain beetle, weevils	Solution	Surface spot spray, crack and crevice spray: hand held sprayers	10 g/L of spray	Not stated	Not stated	Not stated	Yes

Site(s)	Pest(s)	Formulation Type	Application Methods and Equipment	Application Rate (g a.i.)		Maximum Number of Applications per Year	Minimum Number of Days Between Applications	Registrant Supports the Use?
				Maximum Single	Maximum Cumulative			
Use Site Category # 20: Structural; and/ or Use Site Category # 33: Residential Outdoors								
Food handling areas, food processing plants, meat packing plants (excluding when plant is in operation) Homes, hospitals, hotels, motels, restaurants, storage areas, utilities, warehouses Boats, buses, ships, trains - transportation equipment	Ants, booklice, brown dog tick, carpenter ants, carpenter bee, carpet beetles, centipedes, cockroaches, crickets, earwigs, fleas, grain weevils, millipedes, sawtooth grain beetle, sowbugs, spiders, silverfish, termites, ticks Exposed adult and larval stages of drug store beetle, flour beetles, grain weevils, chocolate moth Hibernating stages of: boxelder bug, clover mite, cluster fly, elm leaf beetle	Pressurized Product	Surface spot spray, crack and crevice spray: pressurized can	Not stated	Not stated	Not stated	Not stated	Yes

Site(s)	Pest(s)	Formulation Type	Application Methods and Equipment	Application Rate (g a.i.)		Maximum Number of Applications per Year	Minimum Number of Days Between Applications	Registrant Supports the Use?
				Maximum Single	Maximum Cumulative			
Buildings (outside surfaces), garages, porches, screen doors, window frames	Flies	Emulsifiable concentrate	Surface spot spray, crack and crevice spray: hand held sprayers and pressurized can	11.7 g/L	Not stated	Not stated	Not stated	Yes
		Pressurized product		Not stated	Not stated	Not stated	Not stated	
		Solution		10 g/L of spray				
	Mosquitoes	Solution		10 g/L of spray	Not stated	Not stated	Not stated	No
	Punkies	Emulsifiable concentrate		11.7 g/L	Not stated			
Commercial locations, industrial locations, institutional locations (outside surfaces)	Mosquitoes, punkies, sandflies	Solution	Surface spot spray, crack and crevice spray: hand held sprayers	10 g/L of spray	Not stated	Not stated	Not stated	No
Use Site Category # 20: Structural; and/ or Use Site Category # 33: Residential Outdoors								
Hornets nests, wasp nests	Hornets, wasps	Emulsifiable concentrate	Surface spot spray, crack and crevice spray: hand held sprayers and pressurized can	Not stated	Not stated	Not stated	Not stated	Yes
		Solution						
		Pressurized Product		Not stated	Not stated	Not stated	Not stated	Yes
Bee nests, yellow jacket nests	Bees, hornets, wasps, yellow jackets	Pressurized Product	Surface spot spray, crack and crevice spray: pressurized can	Not stated	Not stated	Not stated	Not stated	Yes
Outdoors (excluding vegetation and where food is prepared, handled or stored)	Brown dog tick, clover mite, crickets, earwigs, fleas, flies, gnats, millipedes, sowbugs, ants hornets, wasps	Solution	Surface spot spray, crack and crevice spray: hand held sprayers	Not stated	Not stated	Not stated	Not stated	Yes

Site(s)	Pest(s)	Formulation Type	Application Methods and Equipment	Application Rate (g a.i.)		Maximum Number of Applications per Year	Minimum Number of Days Between Applications	Registrant Supports the Use?
				Maximum Single	Maximum Cumulative			
Use Site Category # 25 Human Habitat and Recreational Areas								
Outdoors (excluding animal feeding areas, such as pastures and other foraging areas, water supplies, streams, lakes, or ponds)	Mosquitoes	Emulsifiable concentrate	Aerial application: low volume sprays Ground application: mist blowers	81 g/ha	Not stated	Not stated	Not stated	No
Outdoors	Black flies, mosquitoes	Solution	Ground: aerosol and foggers and ULV equipment	27g/ha	Not stated	Not stated	Not stated	No
			Aerial application: low volume sprayers and ultra low volume (ULV)	132 g/ha				

Appendix IIb Domestic Class uses of propoxur registered in Canada, excluding uses of discontinued products or products with a submission for discontinuation as of January 28, 2009.

Site(s)	Pest(s)	Formulation Type	Application Methods and Equipment	Application Rate (g a.i.)		Maximum Number of Applications per Year	Minimum Number of Days Between Applications	Use Supported by the Registrant?
				Maximum Single	Maximum Cumulative			
Use Site Category # 24: Companion Animals								
Cats (Excluding sick or nursing animals, or on cats under 12 weeks of age, or animals receiving drugs or other pesticide treatments)	American dog tick, brown dog tick, cat flea, dog flea, flea eggs	Slow release	Pet collar	0.5 to 1.5 g /animal	4.5 g /animal (assuming 3 collars used per year)	Not stated	Replace collar no more than once every 4 months	Yes
Dogs (Excluding sick or nursing animals, or on dogs under 12 weeks of age, or animals receiving drugs or other pesticide treatments)				1.185 to 4.26 g /animal	25.56 g /animal (assuming 6 collars used per year)		Replace collar no more than once every 2 months	

Site(s)	Pest(s)	Formulation Type	Application Methods and Equipment	Application Rate (g a.i.)		Maximum Number of Applications per Year	Minimum Number of Days Between Applications	Use Supported by the Registrant?
				Maximum Single	Maximum Cumulative			
Use Site Category # 20: Structural								
Indoors	Ants, beetles (exposed stages), book lice, brown dog tick, carpet beetles, centipedes, cockroaches, crickets, earwigs, firebrats, fleas, flies, millipedes, saw toothed grain beetle (exposed stage), silverfish, spiders, weevils (exposed stages)	Solution	Surface spot spray, crack and crevice spray	Not stated	Not stated	Not stated	Not stated	Yes
	Ants, bees, brown dog tick, carpet beetles, centipedes, cockroaches, crickets, earwigs, fleas, hornets, millipedes, saw toothed grain beetle (exposed stage), silverfish, sowbugs, spiders, ticks	Pressurized product	Surface spot spray, crack and crevice spray	Not stated	Not stated	Not stated	Not stated	Yes
	cockroaches	Paste	Bait station	0.024 g /m^2	Not stated	Not stated	2 months	Yes

Site(s)	Pest(s)	Formulation Type	Application Methods and Equipment	Application Rate (g a.i.)		Maximum Number of Applications per Year	Minimum Number of Days Between Applications	Use Supported by the Registrant?
				Maximum Single	Maximum Cumulative			
Use Site Category # 20: Structural; and/or Use Site Category // 33: Outdoor residential								
Outdoors	American dog tick, brown dog tick, ants, bees, carpet beetles, clover mite, cockroaches, crickets, earwigs, fleas, millipedes, silverfish, sowbugs, spiders, ticks, bee nests, hornet nests, wasp nests, yellow jacket nests, stinging insect nests	Pressurized product	Surface spray (spot and broadcast), crack and crevice spray	Not stated	Not stated	Not stated	Not stated	Yes
	Mosquitoes, gnats							No
Use Site Category // 33: Outdoor residential								
Outdoors	Black flies (adults), mosquitoes (adults)	Solution	Fogger	0.0025 g/m^2	Not stated	Not stated	Not stated	No

Appendix III Commercial Class uses of propoxur registered in Canada, for which information on value is sought

Site(s)	Pest(s)	Use is Support by the Registrant	Concerns from Risk Assessments	Identification of Risk Assessment Concerns
Use Site Category 25 Human Habitat and Recreational Areas				
Commercial locations, industrial locations, institutional locations (outside surfaces)	Mosquitoes, punkies, sandflies	No	Not applicable	Not applicable
Buildings (outside surfaces), garages, porches, screen doors, window frames	Mosquitoes, punkies	No	Not applicable	Not applicable
Outdoors	Black flies, mosquitoes	No	Not applicable	Not applicable

Appendix IV Toxicology Assessment for Propoxur

Table 1 Toxicity Profile of Technical Propoxur[a]

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL [mg/kg bw (/day)]	Results/Effects
Metabolism/Toxicokinetic Studies			
Absorption, Distribution, Excretion ICR mouse, ♀ PMRA 1782264	1 mg/kg bw ^{14}C-propoxur by gavage		**Absorption** Rapid absorption in gastrointestinal tract (25% within 1 minute, 74% by 1 hour). At 1 hour, 22% of the recovered unabsorbed dose remained in the stomach, mostly unmetabolized. **Distribution** Found in blood, liver, carcass within 5 minutes, with trace amounts also found in captured CO_2. **Excretion** Rapid excretion primarily through urine (16% within 0.25 hour, 50% within 1 hour).
Absorption, Excretion Rat PMRA 1249746	5 to 8 mg/kg bw ^{14}carbonyl, 1,3-isopropyl ^{14}C-, or 1,3-isopropyl -3H radiolabelled propoxur by gavage		**Absorption:** Rapid absorption. **Excretion:** 85% eliminated within 16 hours [25% as volatile compounds, 60% in urine, very little in faeces.]
Absorption, Excretion 12 or 13-Weeks Wistar rat 5 ♀/group PMRA 1139148	8000 ppm [= 400 mg/kg bw/d] by diet, rats were fasted, followed by 1 mg/kg bw benzene ring labelled ^{14}C-propoxur by gavage. Altromin 1324 or casein diet		**Absorption:** Rapid absorption in blood (peak 0.25 hours after dosing, minimal amount by 24 hours). **Excretion:** Urine: majority recovered within 24 hours [30-40% (<2 hours), 70-80% (<8 hours) of the administered dose]. Within 48 hours, ≥ 84% excreted in urine, < 5% excreted in faeces. Minimal differences in absorption or excretion of propoxur between diets.
Distribution, Excretion Wistar rat 6 ♂ + 1 ♂ for control PMRA 1672408	0 (non-labelled) or 5 mg/kg bw benzene ring labelled ^{14}C-propoxur by gavage.		**Distribution** Within 1 hour there was rapid distribution to almost all tissues. By 8 hours the highest levels were in the kidneys, liver, blood, some portions of the small intestine and lymph fluid. By 24 hours there was a marked decline in tissues (limited to GI tract, bladder, and mucous membranes of the pharyngeal region, with less in liver and kidneys). By 72 hours, there was no or minimal detection in most tissues except for liver, kidneys, and mucous membranes of the pharyngeal tract. **Excretion:** Most eliminated within 24 hours in urine, also some in faeces.

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL [mg/kg bw (/day)]	Results/Effects
Distribution Albino rat 92 ♂ total/ 3 groups (2 i.v. groups not described) PMRA 1723993	50 mg/kg bw propoxur by oral route	**Distribution:** Kidneys (peak concentration at 6 hours, residual amount by 24 hours) > blood (peak ≤ 0.25 hours) and liver (peak at 4 hours) > brain (peak at 1 hour)	
Distribution 6-Weeks Albino rat 6 ♂ + (6 ♂ interim kills at 2 hours, 1-, 2-, or 4-weeks) PMRA 1723995	30 mg/kg bw/day (2 - weeks) and 50 mg/kg bw/day (next 4-weeks) by gavage. Measured propoxur or metabolite 2-isopropoxyphenol (M2) in kidney, liver, blood, brain, and urine.	**Distribution:** Kidneys > liver > blood > brain Accumulation in kidney over 14 days in contrast to other tissues. M2 had a similar distribution, also increased with time in blood and kidneys, but not to the same extent as parent compound.	
Metabolism 8-Week NMRI mouse 20/sex/group PMRA 1139187	≥ 99.6% purity 0 or 8000 ppm (= 1200 mg/kg bw/day) by diet.	**Metabolism:** 15 metabolites isolated in free form and conjugated with glucuronide and sulphate. The principle metabolite is 2-isopropoxy-5-hydroxyphenyl-methylcarbamate (M6). A large quantity of 2-isopropoxy-5-hydroxy-phenyl-hydroxymethylcarbamate was also found (MS3). Other metabolites found in both sexes were: 1, 2-dihydroxybenzene (M1) 2-isopropoxyphenol (M2) 2-hydroxyphenyl-methylcarbamate (M3) 2-isopropoxyphenyl-carbamic acid (M4) 2-isopropoxy-4-hydroxyl-phenyl methylcarbamate (M4A) 2-isoproxpoxyphenyl-hydroxymethylcarbamate (M5) 1, 5 -dihydroxy-2-isopropoxybenzene (M7) 1, 3,-dihydroxy-2-isopropoxybenzene (M8) Two metabolites [2-isopropoxy-3-hydroxy-phenyl methylcarbamate (M7A), and 2-isopropoxy-4(5)-methoxy-5-phenyhydroxyphenyl-methylcarbamate (M7B)] were found only in females. Also found nitrosated isopropoxy-4-nitrobenzene (M9A).	
Metabolism Long-Evans rat PMRA 1782265	^{14}C-propoxur by gavage.	**Metabolism:** Urine: 34% unchanged, 8% M2, 5% M3, 52% unidentified Faeces: 37% unchanged, 40% M2, 9% M3, 15% unidentified	

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL [mg/kg bw (/day)]	Results/Effects
Metabolism, Excretion 4-Week Wistar rat 5 ♀/group PMRA 1139188	0, 50, 250, or 5000 ppm (= 0, 2.5, 12.5, or 250 mg/kg bw/day) propoxur by diet, followed by a single gavage dose of 1 mg/kg bw ^{14}C-propoxur. The highest dose was repeated for identification of conjugates.		**Metabolism:** Urine: 9 metabolites identified including M3 (22.2%), M2 (17.2%), M7 (14.0%), M1 (7%), M7A(5.9%). Smaller quantities (<5%) were identified for M5, M6, M8, and MS3. All metabolites were conjugated with glucuronide (M3, M2, M7, M1, M5, M6) or sulphate (M3, M2, M7, M1, M7A, M8). It was unclear whether MS3 was conjugated with glucuronide or sulphate. **Excretion:** ≥ 90% in urine No difference between doses or diet (semisynthetic casein or Altromin feed) in identity of metabolites.
Metabolism 13-Week Wistar rat 1) Not stated 2) 10 ♂/group 3) 10 ♂/group PMRA 1139186	0 or 8000 ppm (= 400 mg/kg bw/day) by diet.		**Metabolism:** Urine 1) 9 metabolites identified M1, M2, M3, M4, M5, M6, 2-isopropoxy-5-hydroxy-phenyl carbamic acid (M6CII), M7, MS3. 2) 2 additional metabolites identified (M7A and M8). 3) 8 additional metabolites in low concentrations identified [M4A, MS4, M7B, M7C (a mixture of 2 isomeric compounds following HCl hydrolysis), M9A, M12, M14, M10]. Metabolites formed from depropoxylation, hydrolysis of the ester bond, N-methyl hydroxylation and demethylation, and ring hydroxylation at ring positions 3, 4, and 5. Found nitrosated metabolite M9A.
Metabolism, Excretion 20-Week Wistar rat 5 ♀/group PMRA 1139185	50, 250, or 5000 ppm (= 2.5, 12.5, or 250 mg/kg bw/day) propoxur by diet, followed by a single gavage dose of 1 mg/kg bw ^{14}C-propoxur		**Metabolism:** Urine: 11 metabolites identified, representing 80-86% of the activity. The principal metabolite was M3 (>25%). There was a dose-dependent shift from 3-hydroxylation (M7A) to 5-hydroxylation (M6, M6CII, and M7) metabolites with increasing dosage. Other metabolites identified were M1, M2, M3, M4, M5, M8, and MS3. **Excretion:** Urine: 95 - 97% at 48 hours; most within 24 hours Faeces: 3.2 - 3.5% at 48 hours
Metabolism 52-Week Syrian Gold hamster 10 ♀/group PMRA 1139158	≥ 99.6% purity 0 or 8000 ppm (= 0 or 985 mg/kg bw/day) by diet		**Metabolism:** Urine: 14 metabolites isolated in free form and/or conjugated with glucuronide and sulphate. The principle metabolite is M6. A glucuronide of pyrocatechol monomethyl ether (M13) is a degradation product uniquely observed in hamsters. Other metabolites identified were M1, M2, M3, M4, M4A, M5, M7, M7A, M7B, M7C, M9A, M10 (mercapturic acid conjugate of M5). Depropoxylation, hydrolysis of the ester bond, N-methyl hydroxylation and demethylation, ring hydroxylation at ring positions 3, 4, and 5. Found nitrosated metabolite M9A.
Metabolism 12-Week Rhesus monkey 3/sex/test group + 1/sex/control group	99.6% purity 0 or 40 mg/kg bw/day by gavage.		**Metabolism:** Urine: 11 metabolites isolated in both sexes in free form and/or conjugated with glucuronide and sulphate (M1, M2, M3, M4, M4A, M5, M6, M7, M7B, M9A, M12). M7E was detected only in ♂. Sulfate conjugated form of M5 was only detected in ♀.

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL [mg/kg bw (/day)]	Results/Effects
PMRA 1139169		Depropoxylation, hydrolysis of the ester bond, N-methyl hydroxylation and demethylation, ring hydroxylation at ring positions 4, and 5 (preferential); NOT at position 3 as in the rat. Found nitrosated metabolite M9A.	
Metabolism *In vitro* Liver-cell Fractions Wistar rat, NMRI mouse, DSN hamster, Rhesus monkey (2/sex), Human (6) PMRA 1139180	Post-mitochondrial liver fractions were mixed with propoxur and samples incubated < 2 hours. Only looked for the presence of M3, M4, M5, M6, and M7. Also mixed M5 with liver cell fractions under same conditions.	**Metabolism:** M5 is principle metabolite (40-50% or 17-42%, respectively) for the rat or human M3 is principle metabolite (39-51%, 60-63%, 19-27%, respectively) for the mouse, hamster, monkey % propoxur metabolized: Hamster (22-53%) > monkey (20-29%) > rat (12-36%) > mouse (7-10%) > human (3.5%), suggesting a faster rate of transformation in rodents than humans. Rate of transformation ♂ > ♀ in all species (except humans in which subject sex was not known). M5 further metabolized in monkeys (88%), human (69%) and hamsters (24%) but minimally in rats or mice (<2%). **Considered supplementary due to study limitations.**	
In vivo 5-Day, Liver Enzymes Wistar rat 10/sex/dose PMRA 1249818	99.4% purity 0, 15, or 30 mg/kg bw/day by gavage.	≥ 15 mg/kg bw/day: tremors; ↑ rel liver wt (♂) No induction of mixed function oxidases at 3 hours post-dosing (N-demethylase, O-demethylase, cytochrome P-450).	
In vivo 4-Week, Liver Enzymes Wistar rat ♀ PMRA 1723995	0 or 5000 ppm (250 mg/kg bw/day) by diet. Examined liver cytochrome P450 dependent mono-oxygenases. Altromin 1324 or casein diet	250 mg/kg bw/day: ↑ 7-ethoxycoumarin deethylase, ethoxyresorufin deethylase and aldrin epoxidase (2-3 fold at 3 days), slight ↑ cytosolic glutathione-S-transferase Casein diet induced cytochrome P450 dependent mono-oxygenases by similar factor but produced lower absolute numbers for test and control groups.	

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL [mg/kg bw (/day)]	Results/Effects
Acute Toxicity Studies			
Acute oral (gavage) toxicity Wistar rat PMRA 1249807 PMRA 1249812 PMRA 1790586	99.6% purity 10 - 250 mg/kg bw ♂; 5 - 150 mg/kg bw ♀ in Lutrol 10/sex/group		LD_{50} (♂) = 94 mg/kg bw LD_{50} (♀) = 68 mg/kg bw ≥ 50 mg/kg bw: dyspnea, apathy, spasms, salivation, neurotoxic clinical signs appear within 10 min and recovered within 2 days, but animals apathetic for 6 days (♂, ♀); mortality (♀) 75 mg/kg bw: mortality (♂) **High Acute Oral Toxicity**
	98.6% purity 1 - 160 mg/kg bw ♂; 1 - 80 mg/kg bw ♀ in PEG 400 10/sex/group		LD_{50} (♂) = 69 mg/kg bw LD_{50} (♀) = 47 mg/kg bw Convulsions, muscular tremors and spasms, dyspnoea, salivation, dacryohaemorrhea, bristling coat, apathy. Mortalities exhibited patchy lung and distended dark livers, not seen in survivors. **High Acute Oral Toxicity**
	95% purity 50 - 150 mg/kg bw in tylose suspension 10 ♂/group		LD_{50} (♂) = 90 mg/kg bw Restlessness, tremors, muscle spasms, exophthalmos, uncoordination, respiratory paralysis. Mortalities exhibited liver and kidney congestion. **High Acute Oral Toxicity**
Acute dermal toxicity Rat PMRA 1249807	5000 mg/kg bw ♂, ♀		LD_{50} > 5000 mg/kg bw Convulsions, muscular tremors, muscular spasms, dyspnoea, and salivation. **Low Acute Dermal Toxicity**
Acute dermal toxicity Rabbit PMRA 1672408	2000 mg/kg bw 5/sex/group		LD_{50} > 2000 mg/kg bw Muscular fasciculation, transient ↓ motor activity **Low Acute Dermal Toxicity**
Acute inhalation toxicity Wistar rat PMRA 1672408	99.6% purity 4 dose levels (0.0287- 0.498 mg/L) 5/sex/group		LC_{50} > 0.498 mg/L (4 hour exposure) ≥ 0.3304 mg/L: tremors, reduced activity, piloerection, and unpreened hair for ≥ 24 hours **Slight Acute Inhalation Toxicity**
Eye Irritation NZW rabbit PMRA 1672408 PMRA 1723995	99.6% purity 0.1 g 6 ♂		Severe miosis at 1 hour which cleared within 24 hours. **No eye irritation** up to 96 hours.
	99.8% purity 0.1 ml (□ 0.065 g). 6 ♂		Chemosis at 1 hour, ocular discharge and conjunctival redness. **Mild irritation** which cleared up within 48 hours.

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL [mg/kg bw (/day)]	Results/Effects
Skin irritation NZW rabbit PMRA 1672408 PMRA 1723995	99.6% purity 4 hour exposure 6 ♂	**No irritation**	
	99.8% purity 4 hour exposure 6 ♂	**No irritation**	
Skin sensitization Guinea pig PMRA 1249809 PMRA 1672408	99.8% purity Hartley albino guinea pig Buehler Method 15 ♂/ propoxur group, 5 ♂/ control groups	**Non-sensitizer**	
	98.8% purity Pirbright White guinea pig Maximisation test ♂	**Non-sensitizer**	
Short-Term Toxicity Studies			
14-, 29-Week Oral (Dietary) Wistar rat 10 ♀/group/dose/ timepoint [Interim reports for 100-week rat study] PMRA 1139151	99.9% purity 0, 3000, or 8000 ppm [= 0, 212 and 609 mg/kg bw/day] No 3000 ppm group for the 14-week sacrifice. Casein diet.		**≥ 212 mg/kg bw/day:** ↓ weight gain, ↑ rel liver and kidney wt (29-weeks) **609 mg/kg bw/day:** ↓ weight gain, ↑ abs and rel liver and kidney wts (14-weeks) Cholinesterase activity was not measured. **Considered supplementary due to study limitations.**
Oral (Dietary) Beagle dog 4/sex/group PMRA 1721376	≥ 99.5% purity 0, 60, 600, or 1800 ppm [= 0, 2.1/2.0, 22/21, or 67/66 mg/kg bw/day (♂/♀)]	2.1 (♂)	**≥22/21 mg/kg bw/day:** ↓ abs spleen wt, ↑ cholesterol levels (♂) **67/66 mg/kg bw/day:** ↓ albumin levels, ↓ total protein levels; ↓ weight gain and food consumption (♂); ↑ rel liver wt, ↑ cholesterol levels (♀) Cholinesterase activity was not measured.
26-Week Oral (Dietary) Beagle dog 4/sex/group (A bridging study to determine the NOAEL with regard to plasma cholesterol levels) PMRA 1672408 PMRA 1721376	99.4% purity 0 or 70 ppm [= 0 or 2.5/2.7 mg/kg bw/day (♂/♀)]		No definitive treatment effects were found. Cholinesterase activity was not measured. **Considered supplementary due to study limitations.**

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL [mg/kg bw (/day)]	Results/Effects
52-Week Chronic Toxicity Beagle dog 6/sex/group PMRA 1249815	99.4% purity 0, 200, 600, and 1800 ppm (wk 1-40) / 3600 ppm (week 41-44) / 5400 ppm (week 45-52) (= 0, 6.8, 22, or 66/133/199 mg/kg bw/day) in diet	6.8	**≥ 22 mg/kg bw/day:** ↓ weight gain, ↑ plasma cholesterol, ↑ liver N-demethylase **≥ 66 mg/kg bw/day:** ↑ ALT, ↑ SAP, ↑ thrombocyte, leucocyte and reticulocyte counts, ↑ Heinz bodies, ↑ liver and thyroid wt, ↓ thymus wt, atrophy of thymus gland, ↓ PChE **≥ 133 mg/kg bw/day:** vomiting, ↓ FC **199 mg/kg bw/day:** ↑ salivation, spasms, unsteady gait, mortality No effect on BChE or EChE. No adverse effects observed in urinary bladder.
13-Week Oral (gavage) Rhesus monkey 3/sex/group PMRA 1721376	99.6% purity 40 mg/kg bw/day Measured PChE and EChE at weeks 12 and 13.		**40 mg/kg bw/day:** ↓ PChE, ↑ salivation, twitching, rapid respiration, teeth grinding BChE activity was not assessed. No pathological urinary bladder changes, nor hematological or blood chemistry changes. **Considered supplementary due to study limitations.**
13-Week Dermal NZW rabbit 10/sex/dose PMRA 1672408 PMRA 1721376	0, 50, 250, or 1000 mg/kg bw/day, 6 hours/day, 5 days/week	≥ 1000	No treatment-related effects, including BChE, EChE, and PChE.
Neurotoxicity Studies			
Acute neurotoxicity Oral (gavage) Wistar rat 12/sex/group + 6/sex/group for ChE assays PMRA 1748763	99.4% purity 0, 2, 10, 25 mg/kg bw Same doses for satellite groups, except that 4/6 high dose ♂ were dosed at 35 mg/kg bw/day. ChE assessed 0.75 hours post-treatment.	$BMDL_{10}$ = 0.97	**≥ 2 mg/kg bw:** ↓ BChE, ↓ mean body temp; ↓ motor activity (♂); repetitive chewing (♀) **≥ 10 mg/kg bw:** ↓ EChE, abnormal gait, involuntary clonic movements, laboured breathing, ↓ righting reflex, ↓ auditory stimuli response, ↓ grip strength, ↓ tail pinch response Neurotoxic symptoms noted on day 0 post-treatment. No adverse histopathology observed.
Acute neurotoxicity Oral (gavage) Wistar rat 3/sex/group for PChE and EChE assays + 3 ♂/group for BChE assays PMRA 1723989 PMRA 1790586	98.7% purity 15/ 10 (♂/♀), 20, 40, or 60 mg/kg bw. PChE and EChE assessed 0.2 to 3 hours post-dosing. 10, 30, or 40 mg/kg bw. BChE assessed at 0.5 to 5 hours post-dosing.		**≥ 15/10 mg/kg bw:** ↓ EChE and PChE (both had maximum inhibition at 0.3 hours); ↓ BChE (maximum inhibition at 2 hours)(♂) **≥ 20 mg/kg bw:** trembling (recovery by 0.25 hours) **60 mg/kg bw:** mortality (♀) Neuropathology and FOB were not assessed. **Considered supplementary due to study limitations.**

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL [mg/kg bw (/day)]	Results/Effects
Acute neurotoxicity Oral (gavage) Long-Evan rat 10 ♂/dose for motor activity (5 ♂/dose for ChE assay) PMRA 1721370	≥ 99% purity 0 (corn oil), 0.5, 1.1, 3.4, 9.8, and 21.4 mg/kg bw. Motor activity tested in all animals at 0.25 h post-dosing. BChE and EChE activity tested at 0.67 h post-dosing (5 ♂/ dose).	1.1 (♂)	**≥ 3.4 mg/kg bw (♂):** ↓ BChE, ↓ horizontal and vertical activity **≥ 9.8 mg/kg bw (♂):** ↓ EChE
Acute neurotoxicity Oral (gavage) Wistar rat Blood ChE: 24 ♂ (unclear number/group) BChE 10 ♂/group Open field test: 15 ♂/group Active avoidance: 15 ♂/group/test PMRA 1721377	0 (Tween 80%) or 8.3 mg/kg bw for all studies. Assay blood ChE and BChE activity, learning and motor activity between 5 minutes to 2 hours post-dosing		**8.3 mg/kg bw (♂):** ↓ BChE (recovery half-life was 1.4 hours), ↓ ambulation, ↓ rearing, ↓ grooming, ↓ conditioned avoidance response and ↑ latency **Considered supplementary.**
Acute neurotoxicity Oral (gavage) Wistar rat 5/sex/group + (5/sex/group interim kill at 1 and 3 hours) PMRA 1723995 PMRA 1790440	98.6% purity 0, 1, 5, or 25 mg/kg bw ChE assessed 0.5 (PChE and EChE) or 1 hour (BChE) to 3 days post-dosing.		**25 mg/kg bw:** ↓ BChE, ↓ PChE, convulsions, ↓ motility, apathy, bristling coat; ↓ EChE (♂) Maximal BChE, EChE, and PChE inhibition occurred by 1 hour, recovered by 3 hours post-dosing (EChE, PChE) or 3 days (BChE). Onset of cholinergic symptoms also occurred within several hours and lasted for up to 2 days. Neuropathology and FOB were not assessed. **Considered supplementary due to study limitations.**
Acute neurotoxicity Oral (gavage) Wistar rat 6 ♂/group PMRA 1723992	≥ 95% purity 0 or 50 mg/kg bw		**50 mg/kg bw:** ↓ BChE (within 0.25 hour, maximum at 0.5 hour, recovery by 2 hours), neurotoxic symptoms (salivation, involuntary defecation and urination, secretion from the nose, tremors, paralysis of posterior extremities; appear rapidly and recover within 0.3 to 0.6 hour), max concentration propoxur in blood after 0.25 hour and in brain after 1 hour and only trace amounts remained after 6 hours Neuropathology and FOB were not assessed. EChE and PChE were not measured. **Considered supplementary due to study limitations.**

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL [mg/kg bw (/day)]	Results/Effects
Acute ChE Time-Course Assay Oral (gavage) Long-Evan rat 5 ♂ /group /timepoint except 4 ♂/group at 24 hour timepoint PMRA 1721369	99% purity 0 (corn oil) or 20 mg/kg bw propoxur. Assay BChE and EChE 0.5, 1, 1.5, 4, 24 hours post-dosing.		**20 mg/kg bw (♂):** ↓ BChE and ↓ EChE (0.5, 1, 1.5 hours post-dosing) **Considered supplementary.**
1-Week Oral (gavage) Wistar rat 5/sex/group PMRA 1249814	≥ 98.6% purity 0, 15, or 30 mg/kg bw/day		**≥ 15 mg/kg bw/day:** slight convulsions, apathy Neuropathology and FOB were not assessed. Cholinesterase activity was not measured. **Considered supplementary due to study limitations.**
4-Week Oral (gavage) Wistar rat 10/sex/group PMRA 1723989 PMRA 1790586	≥ 95% purity in PEG-400 3, 10, or 30 mg/kg bw/day Measured PChE and EChE 0.25 hours after dosing at 0.5, 1, 2, 3, and 4 weeks. BChE measured 2 hours after final dose.	3	**≥ 10 mg/kg bw/day:** ↓ BChE, ↓ PChE and EChE (constant effect over time, recovered by 5 hours after last dose) **30 mg/kg bw/day:** brief cholinergic signs Neuropathology and FOB were not assessed.
6-Week Oral (gavage) Wistar rat 6 ♂ + (6 ♂ interim kills at 2 hours, 1-, 2-, or 4-weeks) PMRA 1723992	≥ 95% purity 30 mg/kg bw/day for 2 weeks followed by 50 mg/kg bw for 4 weeks Assess whole blood ChE and BChE.		**≥ 30 mg/kg bw/day:** ↓ BChE (recovered between 2 to 4 weeks), ↓ whole blood ChE (recovered by 4 weeks), transient salivation and tremors (first 5 days post-dosing, also seen first 3 days after dose increase) Neuropathology and FOB were not assessed. PChE and EChE were not measured. **Considered supplementary due to study limitations.**

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL [mg/kg bw (/day)]	Results/Effects
13-Week Oral (dietary) Wistar rat 12/sex/group + (12/sex/group with 4-week recovery) PMRA 1723989 PMRA 1723995	99.5% purity 0, 500, 2000, or 8000 ppm [= 0, 33/39, 132/163, 543/703 mg/kg bw/day (♂/♀)] 6/sex/group assessed for ChE and 6/sex/group for microscopic neuropathology effects Recovery study: 0 or 8000 ppm [= 0 or 543/703 mg/kg bw/day (♂/♀)	LOAEL = 33 (♂)	**≥ 33 mg/kg bw/day:** ↓ BChE, ↑ liver cyt-P450 activity (♂) **≥ 132/163 mg/kg bw/day:** ↓ weight gain, slight ↓ grip strength and foot splay; ↓ EChE (♂); ↑ N- and O-demethylase, ↓ BChE (♀) **543/703 mg/kg bw/day:** ↓ pupillary reflex; seizures, ↓ PChE, ↑ N- and O-demethylase, ↑ liver cyt- P450 (♀) Recovery: no treatment-related effects. No adverse neuropathology.
13-Week Oral (dietary) Wistar rat PMRA 1723989 PMRA 1790586	≥ 99.5% purity 250, 750, or 2000 ppm [≈12.5, 37.5, or 100 mg/kg bw/day]		No adverse effect on PChE and EChE. Neuropathology and FOB were not assessed. BChE was not measured. **Considered supplementary due to study limitations.**
4-Week Inhalation Wistar rat 6/sex/group PMRA 1723989	99.6% purity 0, 1.9, 9.6, and 46.7 mg/m3 [= 0, 0.0019, 0.0096, or 0.0467 mg/L], whole body exposure. 6 hours/day, 5 days/week	0.0096 mg/L	**0.0467 mg/L:** ↓ BChE and PChE Unclear whether EChE activity, hematology, clinical biochemistry, or histopathology were measured. FOB was not assessed.
4- or 8-Week Inhalation Wistar rat 5/sex/group PMRA 1723989 PMRA 1723995	99.6% purity 0, 15.3, 45.3, or 139.6 mg/m3 (= 0, 0.0153, 0.453, or 0.1396 mg/L)], nose-only exposure. 6 hours/day, 5 days/week	8-week: LOAEL = 0.0153 mg/L 4-week: NOAEL = 0.0153 mg/L (♀) or 0.0453 mg/L (♂)	**≥ 0.0153 mg/L:** ↓ BChE (week 8) **≥ 0.0453 mg/L:** ↓ PChE (week 8)(♂); ↓ BChE (week 4)(♀) **0.1396 mg/L:** tremors and piloerection (≤ week 2 ♂, ≤ week 8 ♀), ↓ EChE (week 8); ↓ BChE (week 4)(♂) Unclear whether hematology was measured, limited histopathology (no adverse neuropathology was noted). FOB was not assessed. No effect on urinary bladder hyperplasia.
12-Week Inhalation Wistar rat 10/sex/group PMRA 1249797	98.9% purity 0, 5.7, 18.7, or 31.7 mg/m3 (= 0, 0.0057, 0.0187 or 0.0317 mg/L), nose-only exposure. 6 hours/day, 5 days/week Altromin R diet	NOAEL = 0.0187 mg/L	**0.0317 mg/L:** ↓ BChE (week 12), ↓ EChE and ↓ PChE (week 4 and 10) Urinary bladder epithelium was not examined. Neuropathology and FOB were not assessed.

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL [mg/kg bw (/day)]	Results/Effects
Chronic Toxicity/Oncogenicity Studies			
104-Week Chronic toxicity/ Oncogenicity B6C3F1 mouse 50/sex/group + (10/sex/group interim kill at 12 months) PMRA 1139153	99.6% purity 0, 500, 2000, or 8000 ppm (= 0, 114/150, 472/591, 2081/2671 mg/kg bw/day ♂/♀) in diet Altromin diet	114/150	**≥ 472/591 mg/kg bw/day:** ↑ ALT, ↑ abs and rel liver wt, hyperplasia of urinary bladder epithelium; ↑ liver nodules and ↑ hepatocellular adenomas (♂); ↑ ovarian nodules (♀) **2081/2671 mg/kg bw/day:** ↓ weight gain, ↑ HCT and Hb; ↓ inorganic phosphate, protein and albumin, ↑ incidence of ovarian hemorrhage and thrombosis (♀) At 104 weeks (for 0, 114, 472, and 2081 mg/kg bw/day respectively): **Urinary Bladder Hyperplasia** 2/49, 2/49, 5/49, 20/50 (♂) 1/48, 1/48, 6/47, 31/48 (♀) **Hepatocellular Adenoma** 10/49, 10/49, 15/49, and 21/50 (♂), greater than historical range (0/50 to 11/50) from 13 studies. Cholinesterase activity was not measured. **Evidence of Carcinogenicity.**
106-Week Chronic toxicity/ Oncogenicity Wistar rat 50/sex/group + 10/sex/group interim kill at 12 months PMRA 1672408 PMRA 1721376	99.4% purity 0, 200, 1000, 5000 ppm [= 0, 8.23/11.0, 42.0/56.2, 222/293 mg/kg bw/day (♂/♀)] in diet	8.23/11.0 (♂/♀)	**≥ 42.0/56.2 mg/kg bw/day:** ↑ urinary bladder hyperplasia, ↓ weight gain **222/293 mg/kg bw/day:** ↓ FC, ↑ urinary bladder papillomas and carcinomas, neuromuscular changes (slight ↑ sciatic nerve neuropathy and hind limb muscular atrophy), ↑ rel organ wts (heart, lung, liver, kidney), ↓ AST; ↑ rel adrenal and testes wt, ↑ cholesterol (♂) Incidences of slight to severe sciatic nerve neuropathy: 10/37, 9/44, 9/38, 24/34 ♂; 8/38, 12/39, 25/38, 26/34 ♀ for control, low, med, high doses, respectively. At 106 weeks (for 0, 8.23/11.0, 42.0/56.2, 222/293 mg/kg bw/day ♂/♀): **Urinary Bladder Hyperplasia** 1/98, 1/96, 15/99, 92/97 **Urinary Bladder Papillomas** 0/98, 0/96, 1/99, 53/97 **Urinary Bladder Carcinomas** 0/98, 0/96, 0/99, 13/97 **Uterine Adenocarcinomas** 3/50, 4/50, 3/50, 8/50 (♀) Historical incidences from 6 rat studies range from 14.4% to 20.0%. BChE was not measured. **Evidence of Carcinogenicity.**

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL [mg/kg bw (/day)]	Results/Effects
104-Week Oncogenicity Wistar rat 30 ♀/group (only 25 ♀ for 8000 ppm group) + 5 ♀/group interim kill at 1, 2, 3, and 6 months, and 10 ♀/group sacrifice at 12 and 18 months **Onset/Recovery** **1)** 5 ♀/group (13-week exposure, 10-week recovery **2)** 5 ♀/group (2-week exposure) **3)** 5 ♀/group (13-week exposure, 7 week recovery) **4)** 5 ♀/timepoint (0.5, 1, 1.5, 2, 3, or 4 weeks) **5)** 10 ♀ (2-week exposure, 6-week recovery) **6)** 10 ♀ (4-week exposure, 8 week recovery) PMRA 1139152	≥ 99.6% purity 0, 50, 250, 1000, 3000, 5000, or 8000 ppm (= 0, 2.8, 14.5, 58.3, 184, 349, and 639 mg/kg bw/day) in diet Altromin 1321/1324 diet **Onset/Recovery** 1 -3) all dose levels as above 4-6) 8000 ppm (= 639 mg/kg bw/day)		**≥ 58.3 mg/kg bw/day:** urinary bladder hyperplasia **≥ 184 mg/kg bw/day:** urinary bladder papillomas, ↓ weight gain **≥ 349 mg/kg bw/day:** urinary bladder carcinomas At 104 weeks (for 0, 3, 15, 58, 184, 349, and 639 mg/kg bw/day, respectively): **Urinary Bladder Hyperplasia** 0/29, 0/24, 1/29, 7/25, 17/29, 14/28, 10/20 Onset after 0, 0, 104, 53, 12, 4, 4 weeks, respectively. **Urinary Bladder Papillomas** 0/29, 0/24, 0/29, 0/25, 6/29, 11/28, 6/20 Onset at 184 mg/kg bw/day after 106 weeks. **Urinary Bladder Carcinomas** 0/29, 1/24, 0/29, 0/25, 0/29, 2/28, 4/20 Onset at 349 mg/kg bw/day after 78 weeks. **Onset/Recovery: Urinary bladder hyperplasia:** 1) 639 mg/kg bw/day: 1/5 vs 0/5 for other doses 2) 1/5, 0/5, 0/5, 0/5, 0/5, 1/5, 3/5 for control to high doses, respectively 3) No hyperplasia. 4) 2/5 at 3-week, 3/5 at 4-week, 0/5 for 0.5 to 1.5 week exposure 5 and 6) No hyperplasia. Cholinesterase activity was not measured. **Considered supplementary due to study limitations (focus on urinary bladder effects).**
53-Week Chronic Toxicity Syrian Gold hamster 20 ♀/group + (5 ♀/group interim kill at 1 and 2 months, and 10 ♀/group at 3 and 6 months) PMRA 1139157	≥ 99.6% purity 0, 3000, or 8000 ppm (= 0, 351, or 985 mg/kg bw/day) in diet		**≥351 mg/kg bw/day:** clinical signs (emaciation, poor general condition), ↓ weight gain, ↑ mortality No adverse effects observed in urinary bladder. Cholinesterase activity was not measured. **Considered supplementary due to study limitations.**

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL [mg/kg bw (/day)]	Results/Effects
52- to 55-Week Dermal Oncogenicity Swiss albino mouse 20/sex/group PMRA 1721379	0 or 100 mg/kg bw by dermal application. **Complete carcinogenicity** Propoxur (3x/wk for 51 weeks) **Tumor Initiation** Propoxur (once or 3x/wk for 3 wks) + TPA (3x/wk for 51 weeks) **Tumor Promotion** DMBA + Propoxur (3x/wk for 51 weeks) Positive and negative controls included (acetone for complete carcinogenicity, propoxur with acetone and acetone with TPA for tumor initiation, DMBA with acetone and acetone with propoxur for tumor promotion).		**Complete carcinogenicity** **100 mg/kg bw/day:** fur loss, poor hair growth at the site of application, dermatitis, acne-scaly skin, hyperkeratinization, ↓ body weight, ↑ mortality, skin tumors (confined to topical application area) **Tumor Initiation** **100 mg/kg bw/day + TPA:** as above except no hyperkeratinization nor skin tumors **Tumor Promotion** **DMBA + 100 mg/kg bw/day:** dermal lesions as above, ↓ body weight, ↑ mortality, benign squamous cell papillomas and keratoacanthomas **Considered supplementary due to study limitations.**
108-Weeks (Sacrificed after additional 20-Weeks) Inhalation Oncogenicity Wistar rat 45/sex/group + (5/sex/group interim kill at 12, 18, and 25 months) PMRA 1672408 PMRA 1721376	> 99% purity 0, 2.2, 10.4, or 50.5 mg/m3 (= 0, 0.0022, 0.0104, 0.0505 mg/L) for 6.3 hours/day, 5 days/week, whole body exposure.	0.0022 mg/L	**≥ 0.0104 mg/L:** ↓ BChE, ↓ EChE, ↓ PChE; ↑ hepatocellular carcinomas (♂) **0.0505 mg/L:** ↑ urinary bladder papillomas; ↑ hepatocellular adenomas (♂); ↑ urinary bladder carcinomas, weak ↑ uterine adenocarcinomas (♀) **At 108 wks + 5 months recovery** (for control, low, mid, high doses, respectively): **Urinary Bladder Papillomas and Carcinomas** 0/118, 2/117, 1/119, and 3/119 [Urinary bladder papillomas only: 0/58, 0/60, 1/59, 2/60 (♂); 0/60, 0/57, 0/60, 1/59 (♀)] **Hepatocellular adenomas** 2/58, 0/60, 2/59, 6/60 (♂) **Hepatocellular carcinomas** 0/58, 2/60, 1/59, 1/60 (♂) **Uterine adenocarcinomas** 0/47, 2/45, 2/50, 3/47 (♀) **Evidence of Carcinogenicity.**

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL [mg/kg bw (/day)]	Results/Effects
Reproductive and Developmental Toxicity Studies			
Two-generation reproductive toxicity Wistar rat 25/sex/group PMRA 1672408 PMRA 1721376	99.4 % purity 0, 100, 500, 2500 ppm [= 0, 9, 45, 233 mg/kg bw/day] by diet.	Parental Not determined (LOAEL = 9) Reproductive 45 Offspring 45	**Parental** **≥ 9 mg/kg bw/day:** ↓ EChE (P ♂); ↓ BChE (F1 ♀) **≥ 45 mg/kg bw/day:** ↓ body weight (P ♂, F1 ♂, ♀), ↓ EChE (F1, P); ↓ BChE (P ♂), ↓ food consumption (P and F1 ♂), ↓ PChE (F1 ♀) **233 mg/kg bw/day:** ↑ urothelial hyperplasia (2/25 P♂, 8/25 F1♂, 6/25 P ♀, 7/25 F1 ♀), ↓ BChE (F1 ♂, P ♀) **Reproductive** **233 mg/kg bw/day:** ↓ mean implantations/ dam (F1), ↓ mean pups/dam (F1), ↓ pup birth wt (F1, F2) **Offspring** **233 mg/kg bw/day:** ↓ pup weight gain (F1, F2), ↑ mortality (lactating F2 pups, after day 4)
Two-generation reproductive toxicity Wistar rat 25/sex/group PMRA 1672408 PMRA 1721376	99.8 % purity 0, 30, 80 ppm [= 0, 2/3, or 7/8 mg/kg bw/day (♂/ ♀)] by diet.	Parental 2 Reproductive/ Offspring 7	**Parental** **7 mg/kg bw/day:** ↓ EChE (F1 ♂) [EChE inhibition is not usually considered adverse due to the duration of dosing, but in this study there is no indication that BChE was measured, so EChE is used as a surrogate.] **Reproductive/Offspring** No treatment related toxicity.
Teratology study CD-1 mouse 2-13 ♀/group CD rat 2-12 ♀/group PMRA 1723990	Technical purity Mouse: 0, 5, 10, 20, 40, or 60 mg/kg bw/day by gavage on gestation days 6 to 16, sacrificed on gestation day 17. Rat: 0, 5, or 10 mg/kg bw/day (study 1), or 0, 15, 30, or 50 (study 2) by gavage on gestation days 7 to 19, sacrificed on gestation day 20.		**Mouse** **Maternal** **≥ 20 mg/kg bw/day:** ↑ mortality **Developmental** **60 mg/kg bw/day:** ↑ mortality, ↓ fetal wt **Rat (Study 1)** **Maternal** **10 mg/kg bw/day:** ↑ mortality, ↓ weight gain **Developmental** No adverse effects **Rat (Study 2)** **Maternal** **≥15 mg/kg bw/day:** ↑ mortality **50 mg/kg bw/day:** ↓ weight gain **Developmental** No adverse effects **No evidence of teratogenicity.** **Considered supplementary due to study limitations.**

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOA [mg/kg (/day
Teratology study Wistar rat 25 ♀/group PMRA 1672408 PMRA 1721376	99.4% purity 0, 3, 9, or 27 mg/kg bw/day by gavage on gestation days 6 to 15	Mater 3 Developm 27
Teratology study Wistar rat 10 ♀/group (Range-finding study) PMRA 1723989	99.4% purity 0, 5, 10, 30, or 60 mg/kg bw/day by gavage on gestation days 6 to 15. 5 ♀/group tested for ChE on gestation day 15.	
Teratology study Chinchilla rabbit 16 ♀/group PMRA 1672408 PMRA 1721376	99.4 % purity 0, 3, 10, or 30 mg/kg bw/day by gavage on gestation days 6 to 18.	Mater 10 Developm 10
Teratology study Chinchilla rabbit 10 ♀/group (Range-finding study) PMRA 1723989	99.4 % purity 0, 10, 30, or 60 mg/kg bw/day by gavage on gestation days 6 to 18. 5 ♀/group tested for ChE on gestation day 18.	
Teratology study Himalayan rabbit 15 ♀/group PMRA 1721376	99.6% purity 0, 1, 3, or 10 mg/kg bw/day by gavage on gestation days 6 to 18.	

	NOAEL [mg/kg bw (/day)]	Results/Effects
	Maternal 3 Developmental 27	**Maternal** **≥ 9 mg/kg bw/day:** ↑ grooming, ↑ chewing motions and grinding of teeth, ↓ weight gain and food consumption **27 mg/kg bw/day:** ↑ mortality, tremors, ventral recumbency **Developmental** No fetal/embryo toxic effect **No evidence of teratogenicity**.
		Maternal **≥ 5 mg/kg bw/day:** ↓ BChE, ↓ EChE **≥ 10 mg/kg bw/day:** restlessness, tremor, dyspnoea, ↑ grooming, grinding of teeth and excitation **≥ 30 mg/kg bw/day:** slight weight loss and food consumption, ↓ PChE, ↑ mortality **Developmental** No fetal/embryo toxic effect. **No evidence of teratogenicity.** **Considered supplementary due to study limitations.**
	Maternal 10 Developmental 10	**Maternal** **30 mg/kg bw/day:** dyspnoea and restlessness, ↓ weight gain and food consumption, mortality **Developmental** **30 mg/kg bw/day:** slight ↑ post implantation loss, ↓ mean pups/dam, slight ossification delays in some phalanges **No evidence of teratogenicity.**
		Maternal **≥ 10 mg/kg bw/day:** restlessness and chewing, ↓ BChE, ↓ EChE, ↓ PChE **60 mg/kg bw/day:** mortality, dyspnoea, salivation, ventral recumbency, tonic spasms, laboured breathing, watering eyes, prostration **Developmental** No fetal/embryotoxic effects. **No evidence of teratogenicity.** **Considered supplementary due to study limitations.**
		Maternal No maternal toxicity **Developmental** No fetal/embryotoxic effects. **No evidence of teratogenicity.** **Considered supplementary due to study limitations.**

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL [mg/kg bw (/day)]	Results/Effects
Genotoxicity Studies			
In vitro Ames Reversion assay *Salmonella typhimurium Escherichia coli* PMRA 1672408 PMRA 1721376	98.6% purity ≤ 12500 µg/plate ± S9 *S. typhimurium* (TA98, TA100, TA1535, TA1537)		**Negative**
	98.0% purity ≤ 25000 µg/plate ± S9 *S. typhimurium* (TA98, TA100, TA1535, TA1537, TA1538) *E. coli* (Wp2 hcr)		**Negative**
	98.0% purity ≤ 5000 µg/plate ± S9 *S. typhimurium* (TA98, TA100, TA1535, TA1537, TA1538) *E. coli* (Wp2 hcr)		**Negative**
In vitro Mitotic Recombination assay *Saccharomyces cerevisiae* (D7) PMRA 1139140	99.8% purity ≤ 10000 µg/ml ± S9		**Negative**
In vitro Unscheduled DNA Synthesis Primary rat hepatocytes PMRA 1721376	98.5% purity ≤ 1000 µg/ml		**Negative**
In vivo Unscheduled DNA Synthesis Urinary bladder epithelial cells Wistar rat 4 ♀/group PMRA 1721376	0 or 8000 ppm [≈ 400 mg/kg bw/day] for 18 days.		**Negative** 400 mg/kg bw/day: mild to moderate hyperplasia of the bladder epithelium **Considered supplementary due to study limitations.**

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL [mg/kg bw (/day)]	Results/Effects
In vitro Comet Assay Lymphocytes from 1 ♀ 300 lymphocytes/ dose PMRA 1721373	99.4% purity 0 (DMSO), 10, 50, 100, or 200 µg/ml propoxur	≥ 50 µg/ml: ↑ tail intensity and ↑ tail moment **Positive** **Considered supplementary**	
In vitro Chromosome aberration test Chinese hamster ovary cells PMRA 1672408 PMRA 1721376	99.6% purity ≤ 125 µg/ml - S9 ≤1500 µg/ml + S9	**Negative**	
	98.4 %purity ≤ 5000 µg/ml + S9	**Negative**	
	97.8 % purity ≤ 1250 µg/ml - S9 ≤ 5000 µg/ml + S9	**Negative**	
In vivo Sister chromosome aberration test Chinese hamster bone marrow Oral (Gavage) 5/sex/group PMRA 1672408 PMRA 1721376	99.6% purity ≤ 150 mg/kg bw	**Negative**	
	≥ 99.6% purity ≤ 300 mg/kg bw	**Negative**	
	99.4% purity ≤ 300 mg/kg bw	**Negative**	
In vivo Micronucleus assay Mouse bone marrow PMRA 1672408 PMRA 1721380 PMRA 1721381	99.2% purity 2x (5 or 10 mg/kg bw) by gavage (sacrificed after 6 hours). NMRI mouse	**Negative**	
	99% purity 1, 5, or 10 mg/kg bw by gavage or i.p.. 1x (sacrificed after 24 to 72 hours) or 3x (once/day, sacrificed after 24 or 48 hours). BALB/c mouse 5 ♂/group	**Positive** ≥ 1 mg/kg bw/day (oral or i.p., single dose or multiple dose): ↑ micronuclei formation	
	oral: 0, 13, 25, or 50 mg/kg bw i.p.: 0, 6.3, 13, or 25 mg/kg bw. Sacrificed after 24 or 48 hours. Swiss albino mouse 6 ♂/group	**Positive** 25 mg/kg bw/day (oral or i.p.): ↑ micronuclei formation **Considered supplementary due to study limitations.**	

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL [mg/kg bw (/day)]	Results/Effects
Immunotoxicity			
4-Week Immunotoxicity Mouse 10-15/group/test PMRA 1723994	Purity: 98% in 1% methylcellulose solution 0, 0.5, 2, 5 mg/kg bw Assessed cellular and humoral immunological parameters, including the IgM-plaque forming cell (IgM-PFC) assay. Also assayed reversion (PFC, IgG, IgM) 4 weeks after treatment ceased.		**≥ 2 mg/kg bw/day:** ↑ B cells **5 mg/kg bw/day:** ↓ PFC/spleen, ↓ IgG,↓ graft versus host reaction, ↓ T cells,↑ IL-1 activity,↑ proliferation of reticular cells in lymph node and spleen,↑ spleen wt Reversion: return to control levels. Cholinesterase activity was not measured. **Considered supplementary due to study limitations.**
4-Week Immunotoxicity Wistar rat 10-12 ♂/ group/test PMRA 1721384	99.4% purity in groundnut oil 0, 10, 30, or 90 mg/kg bw/day by gavage IgM-PFC, serum antibody titer to ovalbumin, delayed type hypersensitivity (DTH) assay, and leukocyte and macrophage migration inhibition tests.		**≥ 10 mg/kg bw/day:** ↓ leukocyte and macrophage migration, slight ↓ PFC/spleen, slight ↓ serum antibody titer, slight ↓ DTH reaction (♂) **≥ 30 mg/kg bw/day:** ↓ PFC/spleen, ↓ serum antibody titer, ↓ DTH reaction (♂) **90 mg/kg bw/day**: ↓ EChE (♂) PChE and BChE were not measured. **Considered supplementary due to study limitations.**
4-Week Immunotoxicity Wistar rat 10 ♂/group/test PMRA 1721383	99.4% purity in sunflower oil 0, 0.85, 3.4, and 8.5 mg/kg bw/day by gavage. IgM-PFC and DTH assay.		**8.5 mg/kg bw/day:** ↑ rel liver wt, ↓ PFC/spleen (♂) Cholinesterase activity was not measured. **Considered supplementary due to study limitations.**
4-, 9-, or 12-Week Immunotoxicity Wistar rat 8 ♂/group/test PMRA 1721374	99.4% purity in sunflower oil 8.5 mg/kg bw/day by gavage. IgM-PFC and DTH assay.		**8.5 mg/kg bw/day:** ↓ PFC/spleen, ↓ DTH reaction, ↓ thymus wt (♂) Cholinesterase activity was not measured. **Considered supplementary due to study limitations.**

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL [mg/kg bw (/day)]	Results/Effects
Special Studies			
53-Week Toxicity NMRI mouse 20 ♀/group + (5 ♀/group interim kill at 1 and 2 months and 10 ♀/group at 3 and 6 months) PMRA 1139153	≥ 99.6% purity 0, 3000, or 8000 ppm (= 0, 1291, or 3746 mg/kg bw/day) in diet Altromin 1321 diet		**≥ 1291 mg/kg bw/day:** ↑ rel liver wt, fatty degeneration of liver cells (♀) **3476 mg/kg bw/day:** ↓ weight gain (♀) No urinary bladder hyperplasia was observed. Cholinesterase activity was not measured. **Considered supplementary due to study limitations (focus on urinary bladder effects).**
13-Week Toxicity Wistar rat 20 ♀/group + (20 ♀/group with 8 week recovery) [To investigate reversibility of urinary bladder hyperplasias] PMRA 1721376	0 or 8000 ppm (= 0 or 844 mg/kg bw/day) in diet.		**844 mg/kg bw/day:** ↓ body weight, ↓ food consumption, ↑ urinary bladder hyperplasia (♀) **Hyperplasia** (0 and 844 mg/kg bw/day, respectively, ♀): 0/20, 15/20 **Recovery** No urinary bladder hyperplasia, only ↓ body weight. Cholinesterase activity was not measured. **Considered supplementary due to study limitations (focus on urinary bladder effects).**
52-Week Toxicity Sprague-Dawley rat 20 ♀/group + (5 ♀/group interim kill at 1 and 2 months, and 10 ♀/group at 3 and 6 months) [To elucidate strain differences.] PMRA 1139154	≥ 99.6% purity 0, 3000, or 8000 ppm (= 0, 248, and 722 mg/kg bw/day) in diet Altromin 1321 diet		**≥ 248 mg/kg bw/day:** ↓ weight gain, urinary bladder hyperplasia, transient ↑ rel kidney wt (♀) **722 mg/kg bw/day:** vascularization and papillary and nodular hyperplasia (beginning at 4 months), transient ↑ rel liver wt (♀) **Hyperplasia** (at 0, 248, and 722 mg/kg bw/day respectively, ♀): At 4 weeks: 0/5, 2/5, 2/5 At 27 weeks: 0/10, 3/10, 8/10 (1 low dose and 4 high dose animals with neovascularization and 1 high dose animal with papillary hyperplasia) At 52 weeks: 0/19, 3/20, 20/20 Cholinesterase activity was not measured. **Considered supplementary due to study limitations (focus on urinary bladder effects).**

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL [mg/kg bw (/day)]	Results/Effects
100-Week Toxicity Wistar rat 15 ♀/group + (5 ♀/group interim kill at 0.5, 1, and 2 months, and 10 ♀/group at 3 and 6 months) [To investigate diet difference.] PMRA 1139155	≥ 99.6 % purity 0, 3000, or 8000 ppm (= 0, 212 and 609 mg/kg bw/day) in diet Casein semi-synthetic diet		**≥ 212 mg/kg bw/day:** ↓ weight gain, transient ↑ rel liver and kidney wt (♀) **609 mg/kg bw/day:** ↑ rel liver, kidney and lung wt (♀) No urinary bladder hyperplasia. Cholinesterase activity was not measured. **Considered supplementary due to study limitations (focus on urinary bladder effects).**
3-Week Urinary pH study Oral (Dietary) B6C3F1 mouse 10/sex/group [To investigate effects of diet on urinary pH] PMRA 1721376	Commercial rodent diets: Altromin 1324, Ssniff 1/0, Kliba 343, or Purina 5001.		Kliba 343 (mostly casein, starch, glucose): urine was more acidic than other groups on day 13 and 21 (♀) **Considered supplementary due to study limitations.**

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL [mg/kg bw (/day)]	Results/Effects
4-Week Toxicity Wistar rat 5 ♂/group [To investigate effects of urinary pH using NH_4Cl to acidify urine] PMRA PMRA 1721376	0 (corn oil), 8000 ppm [400 mg/kg bw/day] ± 10000 ppm ammonium chloride in diet Examine bladder, kidney, liver, and forestomach by scanning electron microscopy (SEM). Also checked urine for crystals. Altromin 1321 diet		**400 mg/kg bw/day:** ↓ weight gain, ↑ rel kidney wt, hyperplasia of the urinary bladder epithelium (♂) **400 mg/kg bw/day + NH_4Cl:** ↓ urine pH, less severe hyperplasia (♂) **Hyperplasia** (for 0, 400 mg/kg bw/day, 400 mg/kg bw/day + NH_4Cl, respectively), at 4 weeks, ♂: 0/5, 5/5, 2/5 No necrosis or urinary crystals. Cholinesterase activity was not measured. **Considered supplementary due to study limitations (focus on urinary bladder hyperplasia).**
15 Week Wistar rat 15 ♀/group + (10 ♀/group interim kill at 4 weeks) [To investigate effects of urinary pH using NH_4Cl to acidify urine] PMRA 1723989	Technical purity 0 (corn oil), 8000 ppm [≈ 400 mg/kg bw/day] ± 2% ammonium chloride in diet		**0 mg/kg bw/day (+ NH_4Cl):** ↓ body weight, rel ↑ food consumption, ↓ urine pH (weakly acidic), ↑ cytochrome P450, blood vessel dilation in urinary bladder **400 mg/kg bw/day (± NH4Cl):** ↓ body weight, rel ↑ food consumption, ↑ N-demethylase and O-demethylase and cytochrome P450, ↓ beta-glucuronidase, blood vessel dilation in urinary bladder, ↑ rel liver and kidney wt, ↑ urinary bladder hyperplasia **Hyperplasia** at 4 and 15 weeks, respectively, ♀: - NH4Cl: 4/10, 8/14 + NH4Cl: 0/10, 1/15 0 for control animals **Considered supplementary due to study limitations (focus on urinary bladder hyperplasia).**
50-Week Wistar rat 30 ♀/group + (5 ♀/group interim kill at 1, 2, 3, and 6 months) Recovery Study: 9 Week + 6 Week recovery 10 ♀/group [To investigate effects of ascorbic acid, which is present in the Altromin but not in casein diet.] PMRA 1139156	≥ 99.6% purity 0, 1000*, 3000, or 8000 ppm ± 1% ascorbic acid [= 0, 82/83, 287/254, 844/795 mg/kg bw/day (+/- ascorbic acid)] in diet *1000 ppm group started two months later and sacrificed at 48 weeks Recovery Study: 8000 ppm (no ascorbic acid) Altromin 1321 diet		**≥ 287/254 mg/kg bw/day (+/- ascorbic acid):** ↓ weight gain, hyperplasia of the urinary bladder epithelium, urinary bladder papilloma and carcinoma (- ascorbic acid only) **844/795 mg/kg bw/day (+/- ascorbic acid):** bleeding snouts, urinary bladder papilloma and carcinoma (+ ascorbic acid only) Urinary bladder neoplasia [0, 82/83, 287/254, 844/795 mg/kg bw/day (+/- ascorbic acid), respectively]: **Hyperplasia (4 weeks)** +: 0/5, 0/5, 0/5, 4/5 -: 0/5, 0/5, 1/5, 3/5 **Hyperplasia (50 weeks)** +: 0/30,0/30,15/30, 29/30 -: 0/30, 0/28, 21/30, 16/19 **Papilloma (50 weeks)** +: 0/30, 0/30, 0/30, 1/30 - : 0/30, 0/28, 1/30, 1/19 **Carcinomas (50 weeks)** - only: 0/30, 0/28, 1/30, 2/19

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL [mg/kg bw (/day)]	Results/Effects
			Recovery **844/795 mg/kg bw/day (- ascorbic acid):** no effects (0/10), in comparison to 3/5 high dose rats that had urinary bladder hyperplasia sacrificed after 8 weeks with no recovery. Cholinesterase activity was not measured. **Considered supplementary due to study limitations (focus on urinary bladder effects).**
Tolerance study 6-Week CD-1 mouse ≥ 4 ♂/ timepoint/ test PMRA 1721385	98.8% purity ↑ concentrations (50-2000 ppm) on a weekly basis in drinking water. + 10 mg/kg ip propoxur or 0.1 mg/kg bw s.c. oxotremorine + 4.2 mg/kg bw i.p. carbachol. Test BChE and [^{3}H] QNB binding. + assess hexobarbital sleeping times.		Pretreated group had ↑ LD50 (44.5 for pretreated, vs 25.4 for control). Also resistant to hypothermic effect and ↓ body weight effect of propoxur that was seen in non-pretreated group. Suggests tolerance. Pretreatment did not affect response to oxotremorine (muscarinic antagonist), carbachol (cholinergic agonist not affected by cholinesterase), or QNB binding (muscarinic antagonist), and were resistant to BChE inhibition (in comparison 10 mg/kg bw unpretreated with ↓ BChE). Suggests tolerance was not due to ↓ number of cholinergic receptors. ↓ hexobarbital sleeping time in treated animals suggesting (indirectly) that tolerance is induction of hepatic microsomal enzymes. **Considered supplementary due to limited study parameters.**
Metabolite Toxicity Studies - Acute Toxicity			
Acute Oral Rat, ♀ PMRA 1790586	**M3**, in 0.2% aqueous CMC suspension	LD_{50} (♀) [illegible] 1100 mg/kg bw Slightly toxic	
Acute Oral Acute Dermal Sprague-Dawley rat 4/group PMRA 1790586	500 or 1000 mg/kg bw **M2**, in 80% PEG/ 20% ETOH (oral route) or in xylene (dermal route).	LD_{50} (oral, dermal) > 1000 mg/kg bw Slightly toxic	
Metabolite Toxicity Studies - Genotoxicity			
Ames Reversion assay *S. typhimurium* (TA98, TA100, TA1535, TA1537) PMRA 1721376	≤12,500 µg/plate ± S9 **M1**	**Negative**	

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL [mg/kg bw (/day)]	Results/Effects
In vitro Bacterial DNA Damage Test *E. coli* (p 3478, W3110) PMRA 1721376	≤10,000 µg/plate ± S9 **M1**	**Negative**	
Ames Reversion assay *S. typhimurium* (TA98, TA100, TA1535, TA1537) PMRA 1721376	≤12,500 µg/plate ± S9 **M2**	**Negative**	
Mitotic recombination assay *S. cerevisiae* (D7) PMRA 1721376	≤10,000 µg/plate ± S9 **M2**	**Negative**	
Ames Reversion assay *S. typhimurium* (TA98, TA100, TA1535, TA1537, TA1538) PMRA 1721376	≤ 5000 µg/plate ± S9 **M3**	**Negative**	
Ames Reversion assay *S. typhimurium* (TA98, TA100, TA1535, TA1537, TA1538) PMRA 1721376	≤ 5000 µg/plate ± S9 **M4**	**Negative**	
Ames Reversion assay *S. typhimurium* (TA98, TA100, TA1535, TA1537, TA1538) PMRA 1721376	≤ 5000 µg/plate ± S9 **M5**	**Negative**	
Ames Reversion assay *S. typhimurium* (TA98, TA100, TA1535, TA1537) PMRA 1723995	96.5% purity ≤1800 µg/plate ± S9 **M8**	**Negative**	

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL [mg/kg bw (/day)]	Results/Effects
In vivo DNA synthesis assay Wistar rat spleen cells 21-24 ♂/group PMRA 1672408 PMRA 1721376	10 mg/kg propoxur, **M3, M4, M5** given orally to rats, sacrificed at 24 hours		**Positive** (M3, M5) suppressed programmed DNA synthesis **Negative** (M4, propoxur) did not suppress programmed DNA synthesis **Negative** (3 metabolites and propoxur) for unprogrammed DNA synthesis, nucleoid sedimentation or DNA binding.
Possible Metabolite Toxicity Studies			
In vitro Spot test *S. typhimurium* his G46 *In vivo* Micronucleus assay ICR mouse bone marrow cells Oral (Gavage) PMRA 1723991	*In vitro*: Nitrosated propoxur with sodium nitrate (NaNO3), then tested for mutagenicity: ≤ 100 µL/plate *In vivo*: 2x [25 mg/kg bw propoxur + 25 mg/kg bw $NaNO_2$], 24 hours apart, sacrificed 6 hours after final dose.		*In vitro* Positive *In vivo* Negative **Considered supplementary due to study limitations**.
13-Week Wistar rat 20 ♀/group + (10 ♀/group interim kill at 4 weeks) [To investigate effects of nitrosation on urinary bladder hyperplasia] PMRA 1672408 PMRA 1721376	99.6% purity 0 or 8000 ppm [= 851 mg/kg bw/day] ± (0, 50, or 150 ppm) $NaNO_3$ in diet. Semisynthetic diet without vitamin C.		851 mg/kg bw/day (± $NaNO_3$): ↓ weight gain, dilated blood vessels of urinary bladder, ↑ consistency and ↓ transparency of the bladder wall, ↑ rel liver and kidney wt, mild hyperplasia of the urinary bladder epithelium(♀) **Considered supplementary due to study limitations (focus on urinary bladder hyperplasia)**.

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL [mg/kg bw (/day)]	Results/Effects
Ames Reversion assay PMRA 1723989 PMRA 1723995	97% purity ≤ 1000 µg/plate propoxur ≤ 100 µg/plate *N*-nitrosopropoxur *S. typhimurium* (TA98, TA100, TA1535, TA1537)		Negative (propoxur) Positive (*N*-nitrosopropoxur) At 50-100 µg/plate, strongly mutagenic in TA1535, less mutagenic in TA 98 and TA 1537. **Considered supplementary due to study limitations.**
	95% purity ≤ 9.2 µg/plate propoxur and *N*-nitrosopropoxur *S. typhimurium* (TA98, TA100, TA1535, TA1537, TA1538)		Negative (propoxur) Positive (*N*-nitrosopropoxur) ≥ 0.92 µg/plate, mutagenic in TA 100 and TA 1535. **Considered supplementary due to study limitations.**
In vitro Single-strand break assay Human fibroblast PMRA 1721376	95% purity 10^{-5} M propoxur and *N*-nitrosopropoxur		Negative (propoxur) Positive (*N*-nitrosopropoxur) **Considered supplementary due to study limitations.**
In vitro Sister chromatid exchange and micronuclei Human lymphocyte PMRA 1721376	0 (DMSO), 50, 100, or 200 µg/ml propoxur or *N*-nitrosopropoxur (24 hour exposure, 48 hour harvest).		Positive (propoxur) ≥ 50 µg/ml: slight ↑ SCE/cell frequency,↑ micronuclei/1000 cells but no dose relationship Positive (*N*-nitrosopropoxur) ≥ 100 µg/ml: ↑ SCE/cell frequency but no dose relationship,↑ micronuclei/1000 cells **Considered supplementary due to study limitations.**

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL [mg/kg bw (/day)]	Results/Effects
In vitro 1) Cytotoxicity 2) Sister chromatid exchange 3) Chromosome aberration 4) HPRT gene mutation in V79 cells 5) Gap-junction intracellular communication 6) Transformation assay in RTE cells Respiratory cell lines [hamster lung fibroblast V79, primary rat tracheal epithelial cell (RTE)] PMRA 1721382	98.7% purity 1) ≤200/250 µg/ml propoxur (V79/RTE) or ≤ 5/1.6 µg/ml *N*-nitrosopropoxur or NP (V79/RTE); 2) ≤200 µg/ml propoxur and ≤ 0.32 µg/ml NP, expose 2 h, harvest 24 h afterwards 3) ≤ 400 µg/ml propoxur, ≤ 10 µg/ml NP 4) ≤ 128 µg/ml propoxur, ≤ 2.0 NP 5) V79 cell metabolic cooperation assay to detect inhibition of gap-junctional intercellular communication 6) 30-250 µg/ml for propoxur, 0.2 - 1.5 µg/ml for NP	Propoxur Negative- not mutagenic to either V79 and RTE cells (SCE, chromosome aberration, HPRT) Positive - Inhibited gap-junctional intercellular communication *N*-nitrosopropoxur ↑ cytotoxicity in V79 and RTE cells (respectively 2- and 6-fold lower than with propoxur) ≥ 0.01 µg/ml- Positive sister chromatid exchange ≥ 2.5 µg/ml- Positive chromosome aberration ≥ 0.5 µg/ml- Positive hgprt gene mutation ≥ 0.2 µg/ml- Positive cell transformation **Considered supplementary due to study limitations.**	
Human Studies - Considered supplemental due to use of human subjects.			
Metabolism Acute Oral 1 Human, suicidal PMRA 1139150	"Large amounts" of Blattanex EC, a formulation with propoxur by oral ingestion.	Metabolism: Urine: 10 metabolites isolated (M1, M2, M3, M4, M5, M6, M7, M7B, M9A, M12), some conjugated with glucuronide or sulphate. Depropoxylation, hydrolysis of the ester bond, N-methyl hydroxylation and demethylation, ring hydroxylation at ring positions 4 and 5. M6 is the principle metabolite. Found nitrosated metabolite M9A. Suggests M9A synthesized in stomach.	
Distribution and excretion Acute Oral Human 1 ♂, 18 years old PMRA 1723989	Fatal intoxication with Unden, a formulation with propoxur by oral ingestion.	Distribution: Propoxur found in stomach. A metabolite suggested to be M2 was detected in liver, kidney, brain, urine, but not in blood. Excretion: Urine: M2 and conjugated form detected	

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL [mg/kg bw (/day)]	Results/Effects
Excretion Acute Oral Human 6 ♂ PMRA 1723989	92.2 mg/kg bw M2 administered at night. 'Later' 3/6 subjects took 50 mg/kg bw M2.	Excretion Urine: 21.5 - 51% (single dose) or 30% (repeated dose) M2 excreted, most within 8 hours post-dosing.	
Acute or Repeat dose Oral Human volunteers PMRA 1672408	0.36 mg/kg bw by diet 1.5 mg/kg bw by diet, 1 ♂ 5 × (0.15 or 0.2 mg/kg bw) at 0.5 h intervals by diet	0.36 mg/kg bw: ↓ EChE (≤ 0.17 h, recover ≤ 3 hours), stomach discomfort, sweating, blurred vision, facial redness, swelling 1.5 mg/kg bw: ↓ EChE (≤ 0.25 hours, recover ≤ 2 hours), blurred vision and nausea, sweating, ↑ pulse rate and vomitting, sweating, ↑ blood pressure (symptoms maximum at 0.5 -0.75 h post-dosing, recovered ≤ 2 hours) Excretion 45% excreted as M2 in urine (81% of this excreted ≤ 5 hours); an underestimate since vomited ≥ 5 × 0.15 mg/kg: ↓ EChE (recover ≤ 3 hours)	
Acute Inhalation Human volunteers 3 ♂, 1 ♀ PMRA 1723995 PMRA 1723989	100% purity 0.4 - 172 mg/m^3 [= 0 - 0.172 mg/L], 6 hours	≥ 0.078 mg/L: ↓ PChE and EChE (max 0.5 hour after exposure) Excretion Most of M2 excreted ≤ 24 h in urine.	

[a] Effects observed in males as well as females unless otherwise reported.

Table 2 Toxicology Endpoints for Use in Health Risk Assessment for Propoxur

Exposure Scenario	Dose (mg/kg bw/day)	Endpoint	Study	CAF or Target MOE[a]
Acute Dietary, Chronic Dietary, or Non-Dietary Oral	$BMDL_{10}$ = 0.97	Brain cholinesterase inhibition and neurological symptoms.	Acute gavage neurotoxicity rat study.	100
	Acute Reference Dose = 0.0097 mg/kg bw Acceptable Daily Intake = 0.0097 mg/kg bw/day			
Dermal	N/A[b]			
Short- or Intermediate-Term Inhalation	NOAEL = 0.010 mg/L (2.6 mg/kg bw/day)	Brain cholinesterase inhibition at the LOAEL of 0.0467 mg/L (12.7 mg/kg bw/day).	4-week inhalation toxicity study in rats	100
Aggregate[b] (oral, inhalation)	Same route-specific endpoints and MOEs as specified above.			
Cancer (Oral, Aggregate[c])	$Q_1^* = 3.7 \times 10^{-3}$ (mg/kg bw/day) $^{-1}$ based on incidences of urinary bladder papillomas and/or carcinomas in male rats, in a 2-year oral carcinogenicity study.			
Cancer (Inhalation)	$Q_1^* = 4.3 \times 10^{-2}$ (mg/kg bw/day)$^{-1}$ based on hepatocellular adenomas in male rats, in a 2-year inhalation carcinogenicity study.			

[a] Explanation of Abbreviations: CAF = composite assessment factor (combined uncertainty and PCPA factors, dietary scenarios), MOE = margin of exposure (exposure scenarios)

[b] Dermal risk assessments for non-cancer endpoints are not required, based on the lack of treatment-related effects, including effects on cholinesterase, in a subchronic dermal study in rabbits up to the limit dose of 1000 mg/kg bw/day.

[c] Cancer Aggregate for all routes of exposure (oral, dermal, inhalation).

Appendix V Occupational and Residential Mixer, Loader, Applicator and Postapplication Risk Assessment

Table 1 Summary of Use Scenarios and Risks of Concern

Use Scenario [a]	Inhalation Non-Cancer Risk Assessment [b]	Dermal Non-Cancer Risk Assessment [c]	Incidental Oral Non-Cancer Risk Assessment [d]	Inhalation Cancer Risk Assessment [e]	Dermal Cancer Risk Assessment	Incidental Oral Cancer Risk Assessment [f]
Commercial MLA C&C	Risks not of concern	Not required	Not required	Risks not of concern	Risks not of concern	Not required
Commercial Indoor Postapplication C&C	Covered off by residential postapplication C&C	Not required	Not required	Risks of concern based on residential postapplication C&C	Risks of concern based on residential postapplication C&C	Not required
Commercial Outdoor Postapplication	Not required	Not required	Not required	Not required	Not required	Not required
Residential Applicator C&C	Risks not of concern	Not required	Not required	Risks not of concern	Risks not of concern	Not required
Residential Indoor Postapplication C&C	Risk not of concern	Not required	Risks of concern	Risks of concern	Risks of concern	Risks not of concern
Residential Outdoor Postapplication [g]	Not required	Not required	Not required	Not required	Not required	Not required
Residential Bait Tray Applicator and Postapplication [g]	Not required	Not required	Not required	Not required	Not required	Not required
Residential Applicator Pet Collar	Not required	Not required	Not required	Not required	Risks not of concern	Not required
Residential Postapplication Pet Collar	Not required	Not required	Risks of concern	Not required	Risks of concern	Risks of concern

a. MLA – mixer, loader, applicator. C&C – crack and crevice application.
b. Inhalation non-cancer risk assessment not required for pet collars because inhalation exposure to pet collars is considered to be negligible.
c. Dermal non-cancer risk assessment not required based on a lack of treatment related effects from dermal exposure.
d. Incidental oral non-cancer risk assessments not required for commercial and MLA scenarios because children will not be in those situations.
e. Inhalation cancer risk assessment not required for pet collars because inhalation exposure to pet collars is considered to be negligible.
f. Incidental oral non-cancer risk assessments not required for commercial and MLA scenarios because children will not be in those situations.
g. A risk assessment was not required because outdoor residential crack and crevice, spot, structural and stinging insect nest treatments are limited to areas not frequented by, or inaccessible to, children and the potential for postapplication exposure is minimal. Bait tray applicator and postapplication exposure was considered to be negligible because the active ingredient is enclosed in a self-contained unit and is not available for exposure.

Table 2 Short-term Occupational Mixer, Loader, Applicator Inhalation Exposure Estimates and Margins of Exposure

Site	Formulation [a]	Application Equipment [b]	PPE [c]	Application Rate (g a.i./L, g a.i./can) [d]	ATPD (L/day, can/day) [e]	Inhalation exposure (µg/kg bw/day) [f]	Inhalation MOE [g]
Indoors, outdoors, stinging insect nests, commercial, industrial and institutional locations	EC, SN (1% a.i.)	LP Handwand	None	11.70	150	1.13	2294
			Respirator		150	0.11	22943
		HP Handwand	None		3750	94.64	27
			Respirator		3750	9.46	275
			None		700	17.67	147
			Respirator		700	1.77	1472
			None		1200	30.29	86
			Respirator		1200	3.03	858
		Backpack	None		150	1.56	1670
			Respirator		150	0.16	16699
		Paintbrush	None		20	2.48	1046
			Respirator		20	0.25	10464
Stinging insect nests, boats, buses, ships, trains	PP (0.5% a.i.)	Aerosol	None	2.41	6	0.34	7647
			Respirator		6	0.03	76467
Boats, buses, ships, trains	PP (2% a.i.)		None	11.00	6	1.55	1675
			Respirator		6	0.16	16753

a. EC = emulsifiable concentrate, SN = solution, PP = pressurized product.
b. HP = high pressure, LP = low pressure. Mix, load and apply were assessed for HP/LP handwand, backpack and paintbrush, and application was assessed for aerosol.
c. Personal Protective Equipment (PPE); None = no respirator, Respirator = with respirator.
d. An application rate was provided only for the EC formulation. Since the solution formulation has the same percent guarantee as the mixed EC formulation this rate was used for both formulations. No rate was provided for aerosol formulations. The percent guarantee was used along with the can size to determine a rate in g a.i./can. Aerosol formulation application rates are in g a.i./can.

e. ATPD = Area Treated per Day. Aerosol based on 1 container/day/house and a commercial applicator being able to treat 6 houses. Paintbrush based on 4 L/day/house and a commercial applicator being able to treat 5 houses since painting would require more time than aerosol application. Aerosol ATPD are in can/day.

f. Where inhalation exposure (µg/kg bw/day) = (unit exposure × area treated per day × application rate)/70 kg. Inhalation exposure was also calculated using a protection factor of 90% for use of a respirator. Assumes 100% absorption through inhalation.

g. MOE = margin of exposure; Inhalation MOE = inhalation NOAEL/inhalation exposure, based on a short-, intermediate-term inhalation NOAEL of 2.6 mg/kg bw/day and a target MOE of 100. Shaded cells indicate MOEs that are less than the target MOE.

h. Dermal non-cancer risk assessment not required because dermal exposure was not a concern for non-cancer exposure based on a lack of treatment related effects.

Table 3 Dermal Exposure and Cancer Risk Estimates for Commercial Mixer, Loader, Applicators

Site	Formulation [a]	Application Equipment [b]	PPE [c]	Application Rate (g a.i./L, g a.i./can) [d]	ATPD (L/day, can/day) [e]	ADD (mg/kg bw/day) [f]	LADD (mg/kg bw/day) [g]	Cancer Risk [h]	Combined Inhalation and Dermal Cancer Risk [i]	
									Without Respirator	With Respirator
Indoors, outdoors, stinging insect nests, commercial, industrial and institutional locations	EC, SN (1% a.i.)	LP Handwand	Baseline	11.7	150	4.73E-03	8.29E-05	3E-07	4E-07	3E-07
			Mid-level		150	3.69E-03	6.46E-05	2E-07	3E-07	2E-07
			Maximum		150	3.48E-03	6.10E-05	2E-07	3E-07	2E-07
		HP Handwand	Baseline		3750	0.70	1.23E-02	5E-05	N/A	N/A
			Mid-level		3750	0.31	5.39E-03	2E-05	N/A	N/A
			Maximum		3750	0.23	4.02E-03	1E-05	2E-05	2E-05
			Baseline		700	0.13	2.29E-03	8E-06	1E-05	9E-06
			Mid-level		700	0.06	1.01E-03	4E-06	5E-06	4E-06
			Maximum		700	0.04	7.50E-04	3E-06	4E-06	3E-06
			Baseline		1200	0.22	3.93E-03	1E-05	2E-05	2E-06
			Mid-level		1200	0.10	1.73E-03	6E-06	8E-06	9E-07
			Maximum		1200	0.07	1.29E-03	5E-06	7E-06	7E-07
		Backpack	Baseline		150	2.73E-02	4.79E-04	2E-06	2E-06	2E-06
			Mid-level		150	1.30E-02	2.28E-04	8E-07	9E-07	9E-07
			Maximum		150	1.02E-02	1.78E-04	7E-07	8E-07	7E-07
		Paintbrush	Baseline		20	0.04	6.15E-04	2E-06	2E-06	2E-06
			Mid-level		20	0.03	5.41E-04	2E-06	2E-06	2E-06
			Maximum		20	0.03	5.26E-04	2E-06	2E-06	2E-06
Stinging insect nests, boats, buses, ships, trains	PP (0.5% a.i.)	Aerosol	Baseline	2.41	6	6.06E-03	1.06E-04	4E-07	4E-07	4E-07
			Mid-level		6	3.85E-03	6.75E-05	3E-07	3E-07	3E-07
			Maximum		6	3.41E-03	5.98E-05	2E-07	2E-07	2E-07
Boats, buses, ships, trains	PP (2% a.i.)		Baseline	11.00	6	0.03	4.85E-04	2E-06	2E-06	2E-06
			Mid-level		6	0.02	3.08E-04	1E-06	1E-06	1E-06
			Maximum		6	0.02	2.73E-04	1E-06	1E-06	1E-06

a. EC = emulsifiable concentrate, SN = solution, PP = pressurized product.

b. HP = high pressure, LP = low pressure. Mix, load and apply were assessed for HP/LP handwand, backpack and paintbrush, and application was assessed for aerosol.

c. PPE = Personal protective equipment. Baseline PPE = long-sleeved shirt, long pants and chemical resistant gloves, Mid-level PPE = coveralls over long-sleeved shirt, long pants and chemical resistant gloves, Maximum PPE = chemical resistant coveralls over long-sleeved shirt, long pants and chemical resistant gloves.

d. An application rate was provided only for the EC formulation. Since the solution formulation has the same percent guarantee as the mixed EC formulation this rate was used for both formulations. No rate was provided for aerosol formulations. The percent guarantee was used along with the can size to determine a rate in g a.i./can. Aerosol formulation application rates are in g a.i./can.

e. ATPD = area treated per day. Aerosol based on 1 container/day/house and a commercial applicator being able to treat 6 houses. Paintbrush based on 4 L/day/house and a commercial applicator being able to treat 5 houses since painting would require more time than aerosol application. The ATPD for HP handwand was limited to 1200 L/day to achieve acceptable cancer risks. Aerosol ATPD are in can/day.

f. Where absorbed daily dose (ADD) = dermal exposure, as determined by PHED scenarios. Dermal Exposure = (PHED Unit Exposure × Application rate × ATPD × DA)/70 kg. Dermal absorption (DA) factor of 20% applied.

g. Where lifetime average daily dose (LADD) = (ADD × treatment frequency × working duration)/(365 days × 75 years). Treatment frequency = 30 days/year for commercial applicators. Working duration = 16 years.

h. A Q_1^* value of 0.0037 $(mg/kg/day)^{-1}$ was considered appropriate to use in the cancer risk assessment. Shaded cells indicate cancer risks that are more than 1×10^{-5}. Cancer risks equal to or below the cancer risk threshold of 1×10^{-5} were considered to be acceptable.

i. The LADD for both inhalation and dermal exposure were added and then multiplied by the Q_1^* value of 0.0037 $(mg/kg/day)^{-1}$ to obtain combined dermal and inhalation cancer risks. Shaded cells indicate cancer risks that are more than 1×10^{-5}. N/A = not applicable because dermal and inhalation cancer risks were not combined if one or the other exceeds the cancer risk threshold of 1×10^{-5}.

Table 4 Inhalation Exposure and Cancer Risk Estimates for Occupational Mixer, Loader, Applicators

Site	Formulation [a]	Application Equipment [b]	PPE [c]	Application Rate (g a.i./L, g a.i./can) [d]	ATPD (L/day, can/day) [e]	ADD (mg/kg bw/day) [f]	LADD (mg/kg bw/day) [g]	Cancer Risk [h]
Indoors, outdoors, stinging insect nests, commercial, industrial and institutional locations	EC, SN (1% a.i.)	LP Handwand	None	11.70	150	1.13E-03	1.99E-05	9E-07
			Respirator		150	1.13E-04	1.99E-06	9E-08
		HP Handwand	None		3750	9.46E-02	1.66E-03	7E-05
			Respirator		3750	9.46E-03	1.66E-04	7E-06
			None		700	1.77E-02	3.10E-04	1E-05
			Respirator		700	1.77E-03	3.10E-05	1E-06
			None		1200	3.03E-02	5.31E-04	2E-05
			Respirator		1200	3.03E03	5.31E-05	2E-06
		Backpack	None		150	1.56E-03	2.73E-05	1E-06
			Respirator		150	1.56E-04	2.73E-06	1E-07
		Paintbrush	None		20	2.48E-03	4.36E-05	2E-06
			Respirator		20	2.48E-04	4.36E-06	2E-07
Stinging insect nests, boats, buses, ships, trains	PP (0.5% a.i.)	Aerosol	None	2.41	6	3.40E-04	5.96E-06	3E-07
			Respirator		6	3.40E-05	5.96E-07	3E-08

Boats, buses, ships, trains	**PP (2% a.i.)**		**None**	**11.00**	**6**	**1.55E-03**	**2.72E-05**	**1E-06**
			Respirator		**6**	**1.55E-04**	**2.72E-06**	**1E-07**

a. EC = emulsifiable concentrate, SN = solution, PP = pressurized product.

b. HP = high pressure, LP = low pressure. Mix, load and apply were assessed for HP/LP handwand, backpack and paintbrush, and application was assessed for aerosol.

c. PPE = personal protective equipment. None = no respirator, Respirator = with respirator.

d. An application rate was provided only for the EC formulation. Since the solution formulation has the same percent guarantee as the mixed EC formulation this rate was used for both formulations. No rate was provided for aerosol formulations. The percent guarantee was used along with the can size to determine a rate in g a.i./can. Aerosol formulation application rates are in g a.i./can.

e. ATPD = area treated per day. Aerosol based on 1 container/day/house and a commercial applicator being able to treat 6 houses. Paintbrush based on 4 L/day/house and a commercial applicator being able to treat 5 houses since painting would require more time than aerosol application. Aerosol ATPD are in can/day.

f. f Where absorbed daily dose (ADD) mg/kg bw/day = inhalation exposure, as determined by PHED scenarios. Inhalation exposure (mg/kg bw/day) = (unit exposure × area treated per day × application rate)/(70 kg × 1000 µg/mg). Inhalation exposure was also calculated using a protection factor of 90% for use of a respirator. Assumes 100% absorption through inhalation. Inhalation exposure values from Table 2 converted to mg/kg bw/day.

g. Where lifetime average daily dose (LADD) = (ADD × treatment frequency × working duration)/(365 days × 75 years). Treatment frequency = 30 days/year for commercial applicators. Working duration = 16 years.

h. A Q_1^* value of 0.043 $(mg/kg/day)^{-1}$ was considered appropriate to use in the cancer risk assessment. Shaded cells indicate unacceptable cancer risks that are more than 1×10^{-5}. Cancer risks equal to or below the cancer risk threshold of 1×10^{-5} were considered to be acceptable.

Table 5 Short-term Residential Applicator Inhalation Exposure Estimates and Margins of Exposure*

Site	Formulation [a]	Application Equipment [b]	% a.i. [c]	Container Size (L) [c]	Density (kg/L) [d]	Inhalation Exposure (µg/kg bw/day) [e]	Inhalation MOE [f]
Indoors, Outdoors	SN	Handheld Sprayer	1.5	2	1.12	3.06E-03	850340
		Ready-to-use Sprayer	1.5	2	1.12	0.04	69090
		Handheld Pump Sprayer	1.5	2	1.12	0.01	228938
		LP Handwand	1.5	2	1.12	0.02	119838
		Backpack	1.5	2	1.12	0.03	87225
		Paintbrush	1.5	2	1.12	0.36	7303
		Handheld Sprayer	1	4	0.793	2.89E-03	900739
		Ready-to-use	1	4	0.793	0.04	73185
		Handheld Pump Sprayer	1	4	0.793	0.01	242507
		LP Handwand	1	4	0.793	0.02	126940
		Backpack	1	4	0.793	0.03	92395
		Paintbrush	1	4	0.793	0.34	7736
Indoors	SN	Trigger Pump Spray				0.072	36111
	PP	Aerosol				0.27	9630

[a] A pet collar quantitative risk assessment was not required because inhalation exposure to pet collars was considered to be negligible. Dermal non-cancer risk assessment not required due to lack of treatment related effects in animal toxicity study.
a SN = solution, PP = pressurized product.

[b] LP = low pressure; Trigger pump spray and aerosol inhalation exposure were obtained from submitted mixer/loader/applicator exposure studies (Knarr, 1988a; Knarr, 1991), low pressure handwand, backpack and paintbrush inhalation unit exposures are from PHED and handheld sprayer, ready-to-use sprayer and handheld pump sprayer inhalation unit exposures are from ORETF.

[c] Based on verified use information provided by RUAS.

[d] Based on product spec sheets.

[e] Where inhalation exposure (µg/kg bw/day) = (unit exposure × % a.i. × container size × density)/70 kg. Assumes no respirator is worn and there is 100% absorption through inhalation.

[f] MOE = margin of exposure; Inhalation MOE = inhalation NOAEL/inhalation exposure, based on a short-, intermediate-term inhalation NOAEL of 2.6 mg/kg/day and a target MOE of 100.

Table 6 Dermal Exposure and Cancer Risk Estimates for Residential Applicators [a]

Site	Formulation [b]	Application Equipment [c]	% a.i. [d]	Container Size (L) [d]	Density (kg/L) [e]	ADD [f] (mg/kg bw/day)	LADD [g] (mg/kg bw/day)	Cancer Risk [h]	Combined Dermal and Inhalation Cancer Risk [i]
Indoors, Outdoors	SN	Handheld Sprayer	1.5	2	1.12	1.63E-02	7.48E-05	3E-07	3E-07
		Ready-to-use Sprayer	1.5	2	1.12	1.87E-02	8.61E-05	3E-07	3E-07
		Handheld Pump Sprayer	1.5	2	1.12	1.22E-02	5.62E-05	2E-07	2E-07
		LP Handwand	1.5	2	1.12	4.26E-04	1.96E-06	7E-09	8E-09
		Backpack	1.5	2	1.12	9.74E-04	4.48E-06	2E-08	2E-08
		Paintbrush	1.5	2	1.12	4.93E-02	2.27E-04	8E-07	8E-07
		Handheld Sprayer	1	4	0.793	1.53E-02	7.06E-05	3E-07	3E-07
		Ready-to-use	1	4	0.793	1.76E-02	8.12E-05	3E-07	3E-07
		Handheld Pump Sprayer	1	4	0.793	1.15E-02	5.31E-05	2E-07	2E-07
		LP Handwand	1	4	0.793	4.02E-04	1.85E-06	7E-09	7E-09
		Backpack	1	4	0.793	9.20E-04	4.23E-06	2E-08	2E-08
		Paintbrush	1	4	0.793	4.65E-02	2.14E-04	8E-07	8E-07
Indoors	SN	Trigger Pump Spray				0.029	1.34E-04	5E-07	5E-07
	PP	Aerosol				0.056	2.57E-04	1E-06	1E-06

a. Personal protective equipment for residential applicators is assumed to be short pants, short sleeves and no gloves.

b. SN = solution, PP = pressurized product.

c. LP = low pressure; Trigger pump spray and aerosol dermal exposure were obtained from submitted mixer/loader/applicator exposure studies (Knarr, 1988a; Knarr, 1991), low pressure handwand, backpack and paintbrush dermal unit exposures are from PHED and handheld sprayer, ready-to-use sprayer and handheld pump sprayer dermal unit exposures are from ORETF.

d. Based on verified use information provided by RUAS.

e. Based on product spec sheets.

f. Where absorbed daily dose (ADD) mg/kg bw/day = dermal exposure, as determined by PHED, ORETF and submitted studies (Knarr, 1988a; Knarr, 1991). ADD = (% a.i. × container size × density × unit exposure × dermal absorption) / (body weight (70 kg) × 1000 µg/mg). Dermal absorption factor of 20% applied.

g. Where lifetime average daily dose (LADD) = (ADD × Exposure days/year × exposure duration)/(365 days × 75 years). Exposure duration = 63 years. Exposure days per year = 2 days.

h. A Q_1^* value of 0.0037 $(mg/kg/day)^{-1}$ was considered appropriate to use in the cancer risk assessment. Cancer risks equal to or below the cancer risk threshold of 1×10^{-6} were considered to be acceptable. The dermal cancer risk assessment for pet collars can be found in Table 8.

i. The LADD for both inhalation and dermal exposure were added and then multiplied by the Q_1^* value of 0.0037 $(mg/kg/day)^{-1}$ to obtain combined dermal and inhalation cancer risks.

j. Cancer risks equal to or below the cancer risk threshold of 1×10^{-6} were considered to be acceptable.

Table 7 Inhalation Exposure and Cancer Risk Estimates for Residential Applicators a

Site	Formulation [b]	Application Equipment [c]	% a.i. [d]	Container Size (L) [d]	Density (kg/L) [e]	ADD [f] (mg/kg bw/day)	LADD [g] (mg/kg bw/day)	Cancer Risk [h]
Indoors, Outdoors	SN	Handheld Sprayer	1.5	2	1.12	5.77E-06	2.66E-08	1E-09
		Ready-to-use Sprayer	1.5	2	1.12	1.01E-04	4.66E-07	2E-08
		Handheld Pump Sprayer	1.5	2	1.12	1.23E-05	5.64E-08	2E-09
		LP Handwand	1.5	2	1.12	2.17E-05	9.99E-08	4E-09
		Backpack	1.5	2	1.12	2.98E-05	1.37E-07	6E-09
		Paintbrush	1.5	2	1.12	3.56E-04	1.64E-06	7E-08
		Handheld Sprayer	1	4	0.793	5.45E-06	2.51E-08	1E-09
		Ready-to-use	1	4	0.793	9.56E-05	4.40E-07	2E-08
		Handheld Pump Sprayer	1	4	0.793	1.16E-05	5.33E-08	2E-09
		LP Handwand	1	4	0.793	2.05E-05	9.43E-08	4E-09
		Backpack	1	4	0.793	2.81E-05	1.30E-07	6E-09
		Paintbrush	1	4	0.793	3.36E-04	1.55E-06	7E-08
Indoors	SN	Trigger Pump Spray				7.20E-05	3.31E-07	1E-08
	PP	Aerosol				2.70E-04	1.24E-06	5E-08

a. A pet collar quantitative inhalation cancer risk assessment was not required because inhalation exposure to pet collars was considered to be negligible. Personal protective equipment for residential applicators assume no respirator is worn.

b. SN = solution, PP = pressurized product.

c. LP = low pressure; Trigger pump spray and aerosol inhalation exposure were obtained from submitted mixer/loader/applicator exposure studies (Knarr, 1988a; Knarr, 1991), low pressure handwand, backpack and paintbrush inhalation unit exposures are from PHED and handheld sprayer, ready-to-use sprayer and handheld pump sprayer inhalation unit exposures are from ORETF.

d. Based on verified use information provided by RUAS.

e. Based on product spec sheets.

f. f Where absorbed daily dose (ADD) mg/kg bw/day = inhalation exposure, as determined by PHED, ORETF and submitted studies (Knarr, 1988a; Knarr, 1991). ADD = (% a.i. × container size × density × unit exposure) / (body weight (70 kg) × 1000 µg/mg). Assumes 100% absorption through inhalation. Inhalation exposure values from Table 5 converted to mg/kg bw/day.

g. Where lifetime average daily dose (LADD) = (ADD × Exposure days/year × exposure duration)/(365 days × 75 years). Exposure duration = 63 years. Exposure days per year = 2 days.

h. A Q_1^* value of 0.043 $(mg/kg/day)^{-1}$ was considered appropriate to use in the cancer risk assessment.

i. Cancer risks equal to or below the cancer risk threshold of 1×10^{-6} were considered to be acceptable.

Table 8 Dermal Exposure and Cancer Risk Estimates for Residential Applicators of Pet Collars*

Site	Formulation [a]	Application Rate (g a.i./animal) [b]	ADD (mg/kg bw/day) [c]	Exposure Days per Year [d]	LADD [e] (mg/kg bw/day)	Cancer Risk [f]
Dogs	SR	1.175	0.03	2	9.32E-05	3E-07
		1.185	0.03	2	9.40E-05	3E-07
		2.8388	0.08	2	2.25E-04	8E-07
		2.86296	0.08	2	2.27E-04	8E-07
		4	0.11	2	3.17E-04	1E-06
		4.23	0.12	2	3.36E-04	1E-06
		4.266	0.12	2	3.38E-04	1E-06
Cats		1.05	0.03	2	8.33E-05	3E-07
		1.185	0.03	2	9.40E-05	3E-07
		1.5	0.04	2	1.19E-04	4E-07

* An aggregate cancer assessment was not required because inhalation exposure to pet collars was considered to be negligible.

[a] SR = slow release. Clothing worn for pet collar applicators is assumed to be short pants, short sleeves and no gloves.

[b] Based on verified use information provided by RUAS.

[c] Where absorbed daily dose (ADD) mg/kg bw/day = dermal exposure = (application rate (g a.i./animal) × 1 animal/day × fraction a.i. available (1%) × 1000 mg/g × dermal absorption)/70 kg. Dermal absorption factor of 20% applied.

[d] Average of 2 exposure days per year based on seasonal pest pressure.

[e] Where lifetime average daily dose (LADD) = (ADD × Exposure days/year × exposure duration)/(365 days × 75 years). Exposure duration = 38 years.

[f] A Q_1* value of 0.0037 $(mg/kg/day)^{-1}$ was considered appropriate to use in the cancer risk assessment. Cancer risks equal to or below the cancer risk threshold of 1×10^{-6} were considered to be acceptable.

Table 9 Postapplication Inhalation Exposure Estimates and Margins of Exposure from Indoor Crack and Crevice Application*

Exposure Duration	Age category	Air Concentration ($\mu g/m^3$) [a]	Inhalation Exposure (mg/kg bw/day) [b]	MOE [c]
Short-, Intermediate-term	Children	5.1	1.53E-03	1699
	Youth	5.1	1.13E-03	2291
	Adults	5.1	9.69E-04	2683

* An aggregate cancer assessment was not required because inhalation exposure to pet collars was considered to be negligible.

[a] Based on mean overall value from the submitted postapplication study, includes 50 pre-application and 250 postapplication air residue values (Knarr, 1988b)

[b] Where inhalation exposure (mg/kg bw/day) = (air concentration × respiratory rate)/(body weight kg × 1000 µg/mg). Assumes 100% absorption through inhalation. Respiratory rates of 13.3, 8.7 and 4.5 m^3/day and body weights of 70, 39.1 and 15 kg were used for adults, youth and children respectively.

[c] MOE = margin of exposure; Inhalation MOE = inhalation NOAEL/inhalation exposure, based on a short- intermediate-term inhalation NOAEL of 2.6 mg/kg/day. Duration of exposure is uncertain therefore short-and intermediate-term exposures were assessed.

Table 10 Incidental Oral Exposure Estimates and Margins of Exposure for Surface-to-Hand-to-Mouth, Surface-to-Object-to-Mouth and Pet-to-Hand-to-Mouth Transfer to Children

Scenario	Surface	Application Rate ($\mu g/cm^2$) [a]	Transferable Residue ($\mu g/cm^2$) [b]	Incidental Oral Exposure ($\mu g/kg$ bw) [c]	MOE [d]
Surface-to-Hand-to-Mouth Transfer	**Hard**	**52.08**	**5.208**	**13.19**	**74**
	Soft	**52.08**	**2.604**	**13.19**	**74**
Surface-to-Object-to-Mouth Transfer	**Hard**	**52.08**	**5.208**	**0.43**	**2235**
	Soft	**52.08**	**2.604**	**0.22**	**4470**
Scenario	Surface	Application Rate (g a.i./animal) [e]	Transferable Residue ($\mu g/cm^2$) [f]	Incidental Oral Exposure ($\mu g/kg$ bw) [g]	MOE [d]
Pet-to-Hand-to-Mouth Transfer	**Dog (maximum application rate)**	**4.266**	**142.2**	**1801.20**	**1**
	Cat (minimum application rate)	**1.05**	**35**	**443.33**	**2**

a. Based on total deposition from postapplication study (Knarr, 1988b).

b. 5% of the application rate for soft surfaces and 10% of the application rate for hard surfaces (USEPA, 2001)

c. Where surface-to-hand-to-mouth exposure = [(transferable residue × hand surface area (20 cm^2) × hand-to-mouth-events (9.5/hr) × saliva extraction factor (50%) × Duration (8 hrs hard surfaces, 4 hrs soft surfaces)/15 kg] × 10%, and surface-to-object-to-mouth exposure = [(transferable residue × object surface area (25 cm^2) × saliva extraction factor (50%))/15 kg] × 10%. It was assumed that 10% of the area would be treated during a crack and crevice application based on previous assessments and the revised residential SOPs.

d. MOE = margin of exposure; Oral MOE = oral $BMDL_{10}$/oral exposure, based on an oral $BMDL_{10}$ of 0.97 mg/kg/day and a target MOE of 100. Shaded cells indicate MOEs that are below the target MOE of 100.

e. Based on verified use information provided by RUAS.

f. Where transferable residue (TR) = (application rate (g a.i./animal) × 1 animal/day × fraction a.i. available (20%) × 1000000 $\mu g/g$)/surface area of a pet (6000 cm^2).

g. Where pet-to-hand-to-mouth exposure = (TR × hand surface area (20 cm^2) × hand-to-mouth-events (9.5/hr) × saliva extraction factor (50%) × Duration (2 hrs))/ 15 kg.

Table 11 Dermal Exposure and Cancer Risk Estimates for Postapplication Residential Exposure to Indoor Surfaces Following Crack and Crevice Application

Surface	Age Category	ADD [a] (mg/kg bw/day)	Exposure Days per Year [b]	LADD [c] (mg/kg bw/day)	Cancer Risk [d]	Cumulative Lifetime Cancer Risk [e]
Hard	Child	0.17	30	1.10E-03	4E-06	
	Youth	0.06	30	4.20E-04	2E-06	
	Adult	0.10	30	6.86E-03	3E-05	3E-05
Soft	Child	0.17	30	1.10E-03	4E-06	
	Youth	0.06	30	4.20E-04	2E-06	
	Adult	0.10	30	6.86E-03	3E-05	3E-05

[a] Absorbed daily dose (ADD) mg/kg bw/day = dermal exposure = [(application rate × % transferable (10% hard surfaces, 5% soft surfaces) × 0.001 mg/µg × transfer coefficient × exposure time × dermal absorption)/body weight] × 10%; application rate is based on application rate calculated from submitted postapplication study (Knarr, 1988b). Dermal absorption factor of 20% applied. It was assumed that 10% of the area would be treated during a crack and crevice application based on previous assessments and the revised residential SOPs.

[b] Postapplication exposure days/year based on professional judgment.

[c] Lifetime average daily dose (LADD) = (ADD × Exposure days/year × exposure duration)/(365 days × 75 years). Exposure duration = 63 years for adults and 6 years each for children and youths.

[d] A Q_1^* value of 0.0037 $(mg/kg/day)^{-1}$ was considered appropriate to use in the cancer risk assessment. Shaded cells indicate cancer risks that are more than 1×10^{-6}.

[e] Where cumulative lifetime cancer risks = sum of cancer risks from child, youth and adult exposure. Shaded cells indicate cancer risks that are more than 1×10^{-6}.

Table 12 Dermal Exposure and Cancer Risk Thresholds for Postapplication Residential Exposure to Indoor Surfaces Following Crack and Crevice Application

Surface	Age Category	ADD [a] (mg/kg bw/day)	Exposure Days per Year [b]	LADD [c] (mg/kg bw/day)	Cancer Risk [d]	Cumulative Lifetime Cancer Risk [e]
Hard	Child	0.17	1	3.65E-05	1E-07	
	Youth	0.06	1	1.40E-05	5E-08	
	Adult	0.10	1	2.29E-04	8E-07	1E-06
Soft	Child	0.17	1	3.65E-05	1E-07	
	Youth	0.06	1	1.40E-05	5E-08	
	Adult	0.10	1	2.29E-04	8E-07	1E-06

[a] Where absorbed daily dose (ADD) mg/kg bw/day = dermal exposure = [(application rate × % transferable (10% hard surfaces, 5% soft surfaces) × 0.001 mg/µg × transfer coefficient × exposure time × dermal absorption)/body weight] × 10%; Application rate based on application rate calculated from submitted postapplication study (Knarr, 1988b). Dermal absorption factor of 20% applied. It was assumed that 10% of the area would be treated during a crack and crevice application based on previous assessments and the revised residential SOPs.

[b] Maximum exposure days Where cancer risk is below the threshold.

[c] Where lifetime average daily dose (LADD) = (ADD × Exposure days/year × exposure duration)/(365 days × 75 years). Exposure duration = 63 years for adults and 6 years each for children and youths.

[d] A Q_1^* value of 0.0037 $(mg/kg/day)^{-1}$ was considered appropriate to use in the cancer risk assessment. Cancer risks equal to or below the cancer risk threshold of 1×10^{-6} were considered to be acceptable.

[e] Where cumulative lifetime cancer risks = sum of cancers risks from child, youth and adult exposure. Cancer risks equal to or below the cancer risk threshold of 1×10^{-6} were considered to be acceptable.

Table 13 Inhalation Exposure and Cancer Risk Estimates for Indoor Residential Postapplication Exposure Following Crack and Crevice Application

Age Category	ADD (mg/kg bw/day) [a]	Exposure Days per Year [b]	LADD (mg/kg bw/day) [c]	Cancer Risk [d]	Cumulative Lifetime Cancer Risk [e]
Child	**1.53E-03**	**30**	**1.01E-05**	**4E-07**	
Youth	**1.13E-03**	**30**	**7.46E-06**	**3E-07**	
Adult	**9.69E-04**	**30**	**6.69E-05**	**3E-06**	**4E-06**

[a] Where absorbed daily dose (ADD) mg/kg bw/day = inhalation exposure = (air concentration × inhalation rate)/(body weight × 1000 µg/mg); air concentration as determined by submitted postapplication study (Knarr, 1988b). Assumes 100% absorption through inhalation. Inhalation exposure values from Table 9.

[b] Postapplication exposure days/year based on professional judgment.

[c] Where lifetime average daily dose (LADD) = (ADD × Exposure days/year × exposure duration)/(365 days × 75 years). Exposure duration = 63 years for adults and 6 years each for children and youths.

[d] A Q_1^* value of 0.043 $(mg/kg/day)^{-1}$ was considered appropriate to use in the cancer risk assessment. Shaded cells indicate cancer risks that are more than 1×10^{-6}. Cancer risks equal to or below the cancer risk threshold of 1×10^{-6} were considered to be acceptable.

[e] Where cumulative lifetime cancer risks = sum of cancer risks from child, youth and adult exposure. Shaded cells indicate cancer risks that are more than 1×10^{-6}.

Table 14 Inhalation Exposure and Cancer Risk Thresholds for Indoor Residential Postapplication Exposure Following Crack and Crevice Application

Age Category	ADD (mg/kg bw/day) [a]	Exposure Days per Year [b]	LADD (mg/kg bw/day) [c]	Cancer Risk [d]	Cumulative Lifetime Cancer Risk [e]
Child	**1.53E-03**	**12**	**4.02E-06**	**2E-07**	
Youth	**1.13E-03**	**12**	**2.98E-06**	**1E-07**	
Adult	**9.69E-04**	**12**	**2.68E-06**	**1E-06**	**1E-06**

[a] Where absorbed daily dose (ADD) mg/kg bw/day = inhalation exposure = (air concentration × inhalation rate)/(body weight × 1000 µg/mg); air concentration as determined by submitted postapplication study (Knarr, 1988b). Assumes 100% absorption through inhalation. Inhalation exposure values from Table 9.

[b] Maximum exposure days where cancer risk is below the threshold.

[c] Where lifetime average daily dose (LADD) = (ADD × Exposure days/year × exposure duration)/(365 days × 75 years). Exposure duration = 63 years for adults and 6 years each for children and youths.

[d] A Q_1^* value of 0.043 $(mg/kg/day)^{-1}$ was considered appropriate to use in the cancer risk assessment. Cancer risks equal to or below the cancer risk threshold of 1×10^{-6} were considered to be acceptable.

[e] Where cumulative lifetime cancer risks = sum of cancer risks from child, youth and adult exposure. Cancer risks equal to or below the cancer risk threshold of 1×10^{-6} were considered to be acceptable.

Table 15 Dermal Exposure and Cancer Risk Estimates for Postapplication Exposure to Pet Collars

Scenario	Age Category	Application Rate (g/animal) [a]	ADD (mg/kg bw/day) [b]	Exposure Days per Year [c]	LADD [d] (mg/kg bw/day)	Cancer Risk [e]	Cumulative Lifetime Cancer Risk [f]
Dogs Maximum Application Rate	**Child**	**4.266**	**1.14**	**30**	**7.48E-03**	**3E-05**	
	Youth	**4.266**	**0.44**	**30**	**2.87E-03**	**1E-05**	
	Adult	**4.266**	**0.24**	**30**	**1.02E-02**	**4E-05**	**8E-05**
Cats Minimum Application Rate	**Child**	**1.05**	**0.28**	**30**	**1.84E-03**	**7E-06**	
	Youth	**1.05**	**0.11**	**30**	**7.06E-04**	**3E-06**	
	Adult	**1.05**	**0.06**	**30**	**2.50E-03**	**9E-06**	**2E-05**

[a] Based on verified use information from RUAS.

[b] Where absorbed daily dose (ADD) mg/kg bw/day = dermal exposure = (application rate × 1 animal/day × % available for exposure (20%) × % transferable (10%) × 1000 mg/g × dermal absorption)/body weight. Dermal absorption factor of 20% applied.

[c] Postapplication exposure days/year based on professional judgment.

[d] Where lifetime average daily dose (LADD) = (ADD × Exposure days/year × exposure duration)/(365 days × 75 years). Exposure duration = 38 years for adults and 6 years each for children and youths.

[e] A Q_1^* value of 0.0037 $(mg/kg/day)^{-1}$ was considered appropriate to use in the cancer risk assessment. Shaded cells indicate cancer risks that are more than 1×10^{-6}.

[f] Where cumulative lifetime cancer risks = sum of cancer risks from child youth and adult exposure. Shaded cells indicate cancer risks that are more than 1×10^{-6}.

Table 16 Dermal Exposure and Cancer Risk Thresholds for Postapplication Exposure to Pet Collars

Scenario	Age Category	Application Rate (g/animal) [a]	ADD (mg/kg bw/day) [b]	Exposure Days per Year [c]	LADD [d] (mg/kg bw/day)	Cancer Risk [e]	Cumulative Lifetime Cancer Risk [f]
Dogs Maximum Application Rate	**Child**	**4.266**	**1.14**	**1**	**2.49E-04**	**9E-07**	
	Youth	**4.266**	**0.44**	**1**	**9.57E-05**	**4E-07**	
	Adult	**4.266**	**0.24**	**1**	**3.38E-04**	**1E-06**	**3E-05**
Cats Minimum Application Rate	**Child**	**1.05**	**0.28**	**2**	**1.23E-04**	**5E-07**	
	Youth	**1.05**	**0.11**	**2**	**4.71E-05**	**2E-07**	
	Adult	**1.05**	**0.06**	**2**	**1.67E-04**	**6E-07**	**1E-06**

[a] Based on verified use information from RUAS.

[b] Where absorbed daily dose (ADD) mg/kg bw/day = dermal exposure = (application rate × 1 animal/day × % available for exposure (20%) × % transferable (10%) × 1000 mg/g × dermal absorption)/body weight. Dermal absorption factor of 20% applied.

[c] Maximum exposure days where cancer risk is below the threshold or 1, the minimum exposure days per year.

[d] Where lifetime average daily dose (LADD) = (ADD × Exposure days/year × exposure duration)/(365 days × 75 years). Exposure duration = 63 years for adults and 6 years each for children and youths.

[e] A Q_1^* value of 0.0037 $(mg/kg/day)^{-1}$ was considered appropriate to use in the cancer risk assessment. Cancer risks in the range of 1×10^{-6}, were considered to be acceptable.

[f] Where cumulative lifetime cancer risks = sum of cancer risks from child, youth and adult exposure. Shaded cells indicate cancer risks that are more than 1×10^{-6}. Cancer risks equal to or below the cancer risk threshold of 1×10^{-6} were considered to be acceptable.

Table 17 Incidental Oral Exposure and Cancer Risks for Surface-to-Hand-to-Mouth, Surface-to-Object-to Mouth and Pet-to-Hand-to-Mouth Transfer to Children

Scenario	Surface	Application Rate ($\mu g/cm^2$) [a]	Transferable Residue ($\mu g/cm^2$) [b]	ADD [c] (mg/kg bw/day)	Exposure Days per Year [d]	LADD [e] (mg/kg bw/day)	Cancer Risk [f]
Surface-to-Hand-to-Mouth Transfer	**Hard**	**52.08**	**5.208**	**0.01**	**30**	**8.68E-05**	**3E-07**
	Soft	**52.08**	**2.604**	**0.01**	**30**	**8.68E-05**	**3E-07**
Surface-to-Object-to-Mouth Transfer	**Hard**	**52.08**	**5.208**	**4.34E-04**	**30**	**2.85E-06**	**1E-08**
	Soft	**52.08**	**2.604**	**2.17E-04**	**30**	**1.43E-06**	**5E-09**
Scenario	Surface	Application Rate (g/animal) [g]	Transferable Residue ($\mu g/cm^2$) [h]	ADD [i] (mg/kg bw/day)	Exposure Days per Year [d]	LADD [e] (mg/kg bw/day)	Cancer Risk [f]
Pet-to-Hand–to-Mouth Transfer	**Dog (maximum application rate)**	**4.266**	**142.2**	**1.80**	**30**	**1.18E-02**	**4E-05**
	Cat (minimum application rate)	**1.05**	**35**	**0.44**	**30**	**2.92E-03**	**1E-05**
Cancer Thresholds for Pet-to-Hand-to-Mouth Transfer	**Dog (maximum application rate)**	**4.266**	**142.2**	**1.80**	**1**	**3.95E-04**	**1E-06**
	Cat (minimum application rate)	**1.05**	**35**	**0.44**	**4**	**3.89E-04**	**1E-06**

a. Based on total deposition from postapplication study (Knarr, 1988b).
b. 5% of the application rate for soft surfaces and 10% of the application rate for hard surfaces.

c. Where absorbed daily dose (ADD) mg/kg bw/day = oral exposure; Where surface-to-hand-to-mouth exposure = [(transferable residue × hand surface area (20 cm^2) × hand-to-mouth-events (9.5/hr) × saliva extraction factor (50%) × Duration (8 hrs hard surfaces, 4 hrs soft surfaces)/(15 kg × 1000 µg/mg)] × 10% and surface-to-object-to-mouth exposure = [(transferable residue × object surface area (25 cm^2) × saliva extraction factor (50%))/(15 kg × 1000 µg/mg)] × 10%.

d. Postapplication exposure days/year based on professional judgment. Cancer threshold are the maximum exposure days where cancer risk is below the threshold.

e. Where lifetime average daily dose (LADD) = (ADD × Exposure days/year × exposure duration)/(365 days × 75 years). Exposure duration = 6 years for children.

f. A Q_1* value of 0.0037 $(mg/kg/day)^{-1}$ was considered appropriate to use in the cancer risk assessment. Shaded cells indicate cancer risks that are more than 1×10^{-6}. Cancer risks equal to or below the cancer risk threshold of 1×10^{-6} were considered to be acceptable.

g. Based on verified use information provided by RUAS.

h. Where transferable residue (TR) = (application rate × Fraction a.i. Available (20%) × 1000000 µg/g)/surface area of a pet (6000 cm^2).

i. Where ADD mg/kg bw/day = oral exposure; Where pet-to-hand-to-mouth exposure = (TR × hand surface area (20 cm^2) × hand-to-mouth-events (9.5/hr) × saliva extraction factor (50%) × Duration (2 hrs))/ (15 kg × 1000 µg/mg).

Appendix VI Dietary Exposure and Risk Estimates for Propoxur

Table 1 Dietary Exposure and Risk Estimates of Propoxur

Population Subgroup	Acute Dietary Exposure Risk		Chronic Dietary Exposure Risk		Cancer Dietary Exposure Risk	
	Exposure[1] (mg/kg bw) 95th Percentile	% ARD	Exposure[2] (mg/kg bw/day)	% ADI	Exposure[3] (mg/kg bw/day)$^{-1}$	Lifetime Risk
Food-only*						
Canadian Population	0.000155	1.60	0.000055	0.6	0.000055	2E-07
All Infants (< 1 year old)	0.000239	2.46	0.000089	0.9	N/A	N/A
Children 1–2 years old	0.000359	3.70	0.000192	2.0		
Children 3–5 years old	0.000265	2.73	0.000142	1.5		
Children 6–12 years old	0.000167	1.72	0.000086	0.9		
Youth 13–19 years old	0.000108	1.11	0.000050	0.5		
Adults 20–49 years old	0.000080	0.83	0.000039	0.4		
Adults 50+ years old	0.000078	0.81	0.000037	0.4		
Females 13–49 years old	0.00008	0.84	0.000038	0.4		
Toxicological Reference Doses						
[1] Acute Reference Dose (ARfD) = 0.0097 mg/kg bw						
[2] Acceptable Daily Intake (ADI) = 0.0097 mg/kg bw/day						
[3] Cancer Potency Factor (Q_1^*) = 3.7×10^{-3} (mg/kg bw/day)$^{-1}$						

* Highest residue detected in CFIA monitoring database (2002–2008) for domestic products with the inclusion of residues detected in imported commodities, and assuming all food handling establishments in Canada use propoxur.

Appendix VII Food Residue Chemistry Summary

Propoxur was first evaluated by the JMPR in 1973. Its residue and analytical aspects were reviewed in 1977, 1981, 1983, 1991 and 1996.

In 1997, the USEPA completed its re-evaluation of propoxur and published a Reregistration Eligibility Decision [USEPA, 1997]. The California Environmental Protection Agency (Cal/EPA) published a risk characterization document for propoxur [Cal/EPA, 1997].

1 Metabolism and Residue Definition

Metabolism of propoxur in food is adequately understood; the residue of concern is the parent, propoxur.

The residue definition has not been established in Canada for propoxur. The residue of concern in animals and plants is defined as the parent compound by the United States and the JMPR.

Some limited exposure to propoxur residues is possible from the diet because propoxur is used in food handling, storage, and processing establishments.

2 Analytical Methods

An analytical method for propoxur determination in meat and milk was reviewed by PMRA. The method is applicable to the determination of both propoxur and its metabolite o-hydroxyphenyl N-methyl carbamate. The method involves extraction of residues of propoxur and its conjugated metabolite from tissues or milk with a mixture of acetonitrile and hexane. The conjugated metabolite is separated from propoxur by chromatography on a Florisil column. The propoxur residue is hydrolysed with alkali and derivatized with trichloroacetyl chloride. The derivative is cleaned-up by chromatography on silica gel and analysed by GLC using electron capture detection (GLC-ECD). The conjugated metabolite is hydrolysed with acid, derivatized with trichloroacethyl chloride and determined by GLC-ECD. Additional analytical methods were reviewed by PMRA and others were reviewed and reported by the JMPR in 1996.

Multiresidue methods for propoxur determination are published by CFIA [PMR-0010-V1.3] and the United States Food and Drug Administration [Pesticide Analytical Manual, Method 302].

3 Storage Stability

Storage stability data were available on file to support use in food processing and food handling areas (for example, dairy, cereals, meats, prepared foods).

4 Data Gaps

For compliance with the Regulatory Directive DIR98-02, *Residue Chemistry Guidelines*, the following confirmatory residue chemistry studies are required:

DACO 6.2/ DACO 6.3 Nature of the Residue in Food:

MRID 41292301 The nature of the residue in food [Reported in the USEPA DER]

DACO 6.4 Animal Metabolism:

MRID 00142731 Klein, W. (1984) Effect of an Active Ingredient and Three Metabolites on the DNA Metabolism: Report No. A050. Unpublished Mobay Study No. 88852 prepared by Bayer Institute of Toxicology. 36 p.

MRID 40629703 Eben, C. (1986) The Biotransformation of Propoxur in Golden Hamsters: Report No. 93152. Unpublished study prepared by Bayer Ag. 44 p.

MRID 40629702 Eben, C. (1987) Investigations on the Biotransformation of Propoxur in Mice: Report Nos. 15697: 95615. Unpublished study prepared by Bayer Ag. 47 p.

MRID 40629706 Eben, C. (1986) Propoxur (the Active Ingredient of Baygon) Biotransformation Studies on Monkeys: Report No. 94293. Unpublished study prepared by Bayer Ag. 41 p.

MRID 40629704 Eben, C. (1985) Studies on Biotransformation of Propoxur in Humans: Report No. 91951. Unpublished study prepared by Bayer Ag. 39 p.

MRID 41345801 Kao, L. (1989) Disposition and Metabolism of Propoxur in Rats – A Review: Lab Project Number: 99792. Unpublished study prepared by Mobay Corp. 187 p.

JMPR, 1989 Eben, A., Karl, W. & Machemer, L. (1984) Studies on the biotransformation of propoxur in the rat. Unpublished Report No. 12866 (KWN 15) dated August 17, 1984 from Bayer AG Institut für Toxikologie, Wuppertal-Elberfeld. Submitted to WHO by Bayer AG, Leverkusen, Federal Republic of Germany.

DACO 6.2 Livestock Metabolism:

Livestock study Bell, R.L., and R.R. Gronberg, 1975. The metabolic fate of Baygon in the lactating dairy cow. Mobay Study No. 44771. DPR Vol. 50021-106 #920845. [Reported by Review of September 27, 1976 and Cal/EPA, 1997]

Poultry study [Reported by Review of September 27, 1976]

DACO 7.2 Residue Analytical Method:

MRID 42756701 Stanley, C.; Thornton, J. (1990) (Reformat of MRID 121227) Gas Chromatographic Method for Residues of BAYGON and Its Major Metabolite in Animal Tissues and Milk: Lab Project Number: 30451-R: 30451. Unpublished study prepared by Mobay Corp. 18 p.

DACO 7.3 Storage Stability of Residues in/on Food:

MRID 92151030 Storage Information [Reported in the USEPA DER]

DACO 7.4 Magnitude of Residues – Food Handling Establishment:

MRID 42286604 Gronberg, R. (1992) Residues of Baygon in Milk after Treatment of a Dairy Processing Plant with Baygon 70 WP by Crack and Crevice Spot Applications (Addendum I): Lab Project Number: 66123-R-1. Unpublished study prepared by Miles Inc. 6 p.

MRID 42286611 Gronberg, R. (1992) A Gas Chromatographic Method for the Determination of Residues of Baygon in Foods, Foodstuffs and Beverages (Addendum I): Lab Project Number: 54213-R-1. Unpublished study prepared by Miles Inc. 6 p.

[9H5199, 10/16/78] The food additive petition [9H5199, 10/16/78] submitted to the United States and cited in the USEPA RED [1997] including residue data indicating the potential for residues in food adjacent to areas subjected to crack and crevice and spot treatment is required by PMRA to revise the Canadian maximum residue limits of 0.1 ppm [General MRL]

Appendix VIII Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices. There are no MRLs established for propoxur residues in/on any commodity in Canada, in the United States or by the CODEX.

Under the North American Free Trade Agreement, Canada, the United States and Mexico are committed to resolving MRL discrepancies to the broadest extent possible. Harmonization will standardize the protection of human health across North America and promote the free trade of safe food products.

Table 1 Residue Definition in Canada and Other Jurisdictions

Jurisdiction	Residue Definition
Canada	None*
United States	Propoxur
Joint FAO/WHO Meetings on Pesticide Residues	Propoxur

* The residue definition proposed for the risk assessment is the parent, propoxur.

Appendix IX Food Monitoring Data

Canadian Food Inspection Agency Monitoring Data

The National Chemical Residues Monitoring Program of the CFIA monitors pesticide residues in domestic and imported foods. The data is compiled, evaluated and summarized in annual reports. This information is also used to determine the priorities of the ongoing monitoring program. The data allows for assessment of gradual changes in the compliance rate, the effectiveness of introduced control measures, and the estimation of consumer exposure to potentially harmful contaminants. On a daily basis, the results reported are compared to Canadian standards (for example, MRLs). If it is found in violation, the CFIA undertakes actions deemed appropriate to the risk, up to and including product recall.

Propoxur residues found in food monitored by the CFIA during the period from 2002 to 2008 are summarized in the Table 1. The total number of samples analysed during the same period is presented in Table 2. The highest residue detected for Domestic products in the CFIA monitoring database (2002–2008) is 0.002 ppm.

Table 1 Propoxur Residues Reported by CFIA on Domestic and Imported Commodities between 2002 and 2008

Province	Domestic	Imported	Amount	Test Status	Period
Alberta	---	Garlic, Fresh	0.08	---	2002-2003
Alberta	---	Garlic, Fresh	0.07	---	2002-2003
Alberta	---	Garlic, Fresh	0.05	---	2002-2003
British Columbia	---	Garlic, Fresh	0.15	Violation	2002-2003
Ontario	---	Garlic, Fresh	0.063	---	2002-2003
British Columbia	---	Guava, Fresh	0.034	---	2002-2003
British Columbia	---	Garlic, Fresh	0.04	---	2002-2003
British Columbia	---	Garlic, Fresh	0.03	---	2002-2003
British Columbia	---	Grapefruit, Fresh	0.015	---	2002-2003
Ontario	---	Chicory, Fresh	0.025		2004-2005
---	**Cabbage, Fresh**	---	**0.002**	---	**2007-2008**
---	---	Grapefruit, Fresh	0.0017		2007-2008

Table 2 Total Number of Samples Analysed for Propoxur Residues by CFIA between 2002 and 2008

Number of Domestic Samples	Number of Imported Samples	Total Samples	Period
8658	41618	50276	2002-2007
1215	2750	3965	2007-2008

Monitoring data for propoxur are also available from the United States Department of Agriculture's PDP and the European Food Safety Authority (EFSA). No residues of propoxur were detected by PDP (2002-2005) as summarized in Table 3. In 2006, PDP monitored only for residues of propoxur in drinking water but not in food commodities.

Table 3 Propoxur Residues Reported by PDP between 2002 and 2005

Commodity	No Samples	Residue detected	LODRES*	Period
Grape	109	0	0.005	2002-2004
Grape	175	0	0.005	2005
Green Beans	301	0	0.0075	2002-2004
Green Beans	83	0	0.0075	2005
Pears	86	0	0.005	2002-2004
Pears	218	0	0.005	2005
Rice	495	0	0.002	2002-2004
Total Samples	**1467 [0 detects]**			**2002-2005**

* LODRES: value of ½ Limit of Detection

The EFSA 2007 Annual Report on Pesticide Residues reported results of the monitoring of pesticide residues in food commodities analysed during 2007 in the 27 European Union (EU) member states in addition to Norway & Iceland. In total 74,305 samples of approximately 350 different food commodities were analysed for pesticide residues under the national and the EU coordinated programmes (71,936 surveillance samples and 2369 enforcement samples). Detectable propoxur residues in surveillance samples of fruit and vegetables are summarized in Table 4. No propoxur residues were found in/on cereals.

Table 4 Propoxur Detectable Residues Reported by EFSA in Surveillance Samples of Fruit and Vegetables in 2007

Pesticide	No. Samples Sought	No. Samples Found	% Samples Found	LCI*	UCI**
Propoxur	33979	4	0.01	0.00	0.03

* LCI = Lower Confidence Interval
** UCI = Upper Confidence Interval

Appendix X Environmental Fate and Toxicity

Table 1 Fate and Behaviour in the Environment

Property	Test Material	Value	Comments	References
Hydrolysis	**Purity unknown**	**pH 3-7 stable pH 8 $t_{½}$ = 16 d pH 9 $t_{½}$ = 1.6 d**	**Stable under acidic and neutral conditions. Major transformation product : 2-isopropoxyphenol**	**PMRA# 1672408**
Phototransformation - soil	**Purity unknown**	**77 d (extrapolated)**	Photolysis is not an **important route of transformation in soil**	**PMRA# 1672408**
Phototransformation - water	**Purity unknown**	**10 d**	Photolysis may be an important route of transformation in water. Major transformation product : 2-isopropoxyphenol	**PMRA# 1672408**
Soil biotransformation - aerobic	**98-100%**	**Silt loam: 80 Sandy loam: 210**	**Moderately persistent to persistent [1].**	**PMRA# 1672408**
Soil biotransformation - anaerobic	**98-100%**	**Silt loam: 80 Sandy loam: 108**	**Moderately persistent [1].**	**PMRA# 1672408**
Aquatic biotransformation		**No data available for review.**		
Soil Column leaching	**98-100%**	**47-52% of propoxur in leachate after 45 d**	**23% of 2-isopropoxyphenol in the leachate. 7-19% bound residues. Mobile in soil.**	**PMRA# 1672408**
Adsorption/desorption	**98-100%**	**K_d K_{OC} 0.05 3.4 sandy loam 0.30 11.2 silt loam 0.27 102 silt clay**	**Highly to very highly mobile in soil [2]. Potential for leaching into groundwater.**	**PMRA# 1672408**
Field dissipation		**DT50 = 13 d**	**Non persistent. No leaching below 15 cm.**	**PMRA# 1672408**

[1] classified according to the classification of Goring et al (1975)

2 classified according to the classification of McCall et al (1981)

Table 2 Toxicity to Non-Target Species

Organism	Study Type	Species	Test material	Endpoint	Value	References
Terrestrial Species						
Invertebrates	**Acute**	**Honey bee**	**Technical**	**LD50**	**1.34 µg ai/bee**	**PMRA# 1672408**
Birds	**Acute oral**	**Mallard duck**	**98%**	**LD50**	**9.44 mg ai/kg**	**PMRA# 1672408**
		Canada goose	**87%**		**5.95 mg ai/kg**	
		House finch	**97%**		**3.55 mg ai/kg**	
		Dark-eyed junco	**97%**		**4.76 mg ai/kg**	
	Dietary	**Mallard duck**	**99%**	**LC50 NOEC**	**>5000 mg ai/kg diet 1000 mg ai/kg diet**	**PMRA# 1672408**
		Bobwhite quail	**98%**	**LC50 NOEC**	**2828 mg ai/kg diet 1000 mg ai/kg diet**	
	Chronic (repro)	**Mallard duck**	**97%**	**NOEC**	**80 mg ai/kg diet**	**PMRA# 1672408**
		Bobwhite quail	**98%**		**80 mg ai/kg diet**	
Mammals	**Acute oral**	**Laboratory rat**	**70%**	**LD50**	**125 mg ai/kg bw**	**PMRA# 1672408**
		Various rodents	**unknown**	**LD50**	**68-94 mg ai/kg bw**	
	Dietary	**No data**				
	Chronic (repro)	**Laboratory rat**	**99.8%**	**NOEC**	**80 mg ai/kg diet**	**PMRA# 1672408**
Freshwater Organisms						
Invertebrates	**Acute**	**Daphnia magna**	**98.8%**	**48-h LC50**	**11 µg ai/L**	**PMRA# 1672408**
				NOEC	**4.7 µg ai/L**	
		Amphipod	**88%**	**EC50**	**34 µg ai/L**	
		Stonefly			**180 µg ai/L**	
	Chronic	**No data**				
Fish	**Acute**	**Rainbow trout**	**98.8%**	**LC50 NOEC**	**3.7 mg ai/L 2.2 mg ai/L**	**PMRA# 1672408**
		Bluegill sunfish	**98.8%**	**LC50 NOEC**	**6.2 mg ai/L 2.2 mg ai/L**	
		Fathead	**88%**	**LC50**	**25 mg ai/L**	

Organism	Study Type	Species	Test material	Endpoint	Value	References
		minnow				
	Chronic	**No data**				
Marine/Estuarine Organisms						
Invertebrates	**Acute**	**Pink shrimp**	**technical**	**LC50**	**41 µg ai/L**	**PMRA# 1672408**
	Chronic	**No data**				
Fish	**Acute**	**No data**				
	Chronic	**No data**				

Table 3 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient Endpoints	Transformation Products Endpoints
CEPA toxic or CEPA toxic equivalent[1]	**Yes**			
Predominantly anthropogenic[2]	**Yes**			
Persistence[3]:	**Soil**	**Half-life ≥ 182 days**	**Half-life = 26 d**	
	Water	**Half-life ≥ 182 days**	**Half-life = 82 d**	
	Sediment	**Half-life ≥ 365 days**	**Half-life = 95 d (whole system)**	
	Air	**Half-life ≥ 2 days**	**Volatilization is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure (3.3×10^{-5} Pa) and Henry's Law Constant (1.76×10^{-8} Pa × m^3 × mol^{-1}).**	
Bioaccumulation[4]	**Log $K_{ow} \geq 5$**		**-0.969**	
	BCF ≥ 5000		**Not available**	
	BAF ≥ 5000		**Not available**	
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			**No, does not meet TSMP Track 1 criteria.**	**No, does not meet TSMP Track 1 criteria.**

1 All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (i.e. all other TSMP criteria are met).

2 The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

[3] If the pesticide and/or the transformation product(s) meet persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.

[4] Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{ow}).

Appendix XI Water Monitoring Data

A search for propoxur water monitoring data in Canada resulted in five Canadian datasets being identified without any detections being reported. The Federal Provincial and Territorial representatives from all of the provinces and territories in Canada were contacted, requesting water monitoring data for the pesticides that are currently under re-evaluation. In addition, requests were submitted to Environment Canada, the Department of Fisheries and Oceans and the drinking water subcommittee through Health Canada. A response was received by most of provinces and territories indicating that either monitoring data were not available or the available data were submitted.

A report investigating pesticides residues in surface waters of Manitoba since the early 1970's (PMRA 1307573) analyzed approximately 3000 samples over 100 sites in Manitoba. The analyte list included 65 individual fungicides, insecticides and herbicides including propoxur. With a limit of detection of 0.2µg/L, propoxur was not detected out of 548 water samples analyzed.

Series of unpublished data from Manitoba Conservation and Manitoba Water Stewardship (PMRA 1311130 & 1311131) in which pesticides residues were monitored in Manitoba from 1990–2001 and 2001–2003 respectively. A total of 1447 water samples were analyzed in 1990–2001, out of which propoxur was not detected. The analytical method was low in sensitivity with a high limit of detection in the range of 0.2–10µg/L. In 2001–2003, 283 water samples were analyzed with a lower limit of detection of 0.2µg/L and propoxur was not detected.

Unpublished water monitoring data (PMRA 1303803) in which pesticides residues in Saskatchewan were monitored from 1979–2001 was provided to the PMRA. Propoxur was analyzed in a total of 69 water samples, but no detectable concentrations were recorded. The limit of detection ranged from 0.01 to 1.0 µg/L.

In addition to considering the Canadian water monitoring data available, the US databases were searched for detections of propoxur. Available propoxur monitoring data for groundwater and surface water sources were downloaded from the United States Geological Survey National Water Quality Assessment program (NAWQA) database (PMRA 1719746, 1719753). A total of 7266 and 5992 surface and groundwater samples respectively were analyzed for propoxur. Propoxur was detected with a frequency of detection of 1.8 and 0.2% and maximum concentrations of 0.26 and 0.3µg/L in the surface and groundwater samples, respectively. The limit of detection ranged from 0.008–4.104µg/L. In a published study (PMRA 1307555) the occurrence of 75 current-use pesticides and 7 pesticide transformation products was monitored in eight urban streams from across the United States from 1993 to 1994 as part of the U.S. Geological Survey's National Water Quality Assessment Program. Out of a total of 215 filtered water samples, propoxur was detected with a detection frequency of 0.5% and a maximum concentration of 0.26µg/L.

Appendix XII Label Amendments for Products Containing Propoxur

NOTE: The following information is divided according to product type; please read each section carefully and make appropriate changes to the product labels.

The label amendments presented below do not include all label requirements for individual end-use products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. ***Additional information on labels of currently registered products should not be removed unless it contradicts the label statements below.***

A submission to request label revisions will be required within 90 days of finalization of the re-evaluation decision.

A. Technical Class Products

The following warning statement should appear on the PRIMARY PANEL of the technical product labels:

"Caution: Eye Irritant"

B. Commercial Class Products

I. Toxicological Information

"Propoxur is a carbamate which is a cholinesterase inhibitor. Typical symptoms of overexposure to cholinesterase inhibitors include malaise, muscle weakness, dizziness and sweating. Headache, salivation, nausea, vomiting, abdominal pain and diarrhea are often prominent. A life-threatening poisoning is signified by loss of consciousness, incontinence, convulsions and respiratory depression with a secondary cardiovascular component. Treat symptomatically. If exposed, plasma and red blood cell cholinesterase tests may indicate degree of exposure (baseline data are useful). However, if a blood sample is taken several hours after exposure, it is unlikely that blood cholinesterase activities will be depressed, due to rapid reactivation of cholinesterase. Atropine, only by injection, is the preferable antidote. Do not use pralidoxime. In cases of severe acute poisoning, use antidotes immediately after establishing an open airway and respiration. With oral exposure, the decision of whether to induce vomiting or not should be made by an attending physician."

II. DIRECTIONS FOR USE

- Use directions for application to floor surfaces and areas adjacent to cracks and crevices as well as any indoor broadcast or perimeter sprays to floors, walls and pet quarters must be removed from all current Commercial class end-use product labels.
- Directions for the use to control biting flies (including mosquitoes, black flies, sandflies and punkies) must be removed from all current Commercial class end-use product labels.
- Use directions for a low pressure sprayer equipped with a pin stream spray nozzle must be included on Commercial class labels of products formulated as emulsifiable concentrates or solutions.

III. USE LIMITATIONS/RESTRICTIONS:

- Indoor pest control claims must be consistent with crack and crevice uses only.
- The following statements must be added:
  "Apply only as a crack and crevice treatment indoors."
  "Perimeter broadcast sprays are for outdoor use only"
  "Hornet and wasp nest treatment for outdoor use only"
  "Ant trail treatment for outdoor use only"

- For liquid and emulsifiable formulations the following statements must also be added:
  "Do not apply by paintbrush indoors."
  "Apply with a low pressure sprayer equipped with a pin stream spray nozzle for indoor crack and crevice treatment."

IV. ENGINEERING CONTROLS AND PERSONAL PROTECTIVE EQUIPMENT:

"Wear long pants, long-sleeved shirt, chemical resistant footwear, and chemical resistant gloves when mixing, loading and applying propoxur. Pants should be worn outside footwear to prevent pooling within boots.

When more than 8 kg a.i. is handled per day, a respirator is required when applying propoxur using handheld equipment. The maximum kg a.i. handled per day must be limited to 14 kg when applying propoxur using handheld equipment.

Remove protective equipment immediately after handling this product. Wash outside of gloves and footwear before removing. As soon as possible, wash thoroughly and change into clean clothing. Discard clothing and other absorbent materials that have been drenched or heavily contaminated with this products concentrate. Do not reuse them. Contaminated clothing must be laundered separately in hot water before reusing. Wash hands and face thoroughly after handling and before eating, drinking, chewing gum, smoking, or using toilet."

C. Domestic Class Products

I. TOXICOLOGICAL INFORMATION

"This product contains a pesticide that is a cholinesterase inhibitor (anti-cholinesterase compound). Symptoms of human poisoning may include headache, weakness, sweating, blurred vision, nausea and diarrhea. Obtain medical attention or call a poison control centre at once. Atropine is antidotal."

To all Domestic class products, except bait trays:

II. Add to the PRIMARY PANEL:

"For outdoor use only. Do not use indoors"

III. All directions for indoor use must be removed from the labels and the following statements must be added to the DIRECTIONS FOR USE section:

"For outdoor use only. Do not use indoors"

IV. Add to USE PRECAUTIONS:

"Do not spray on animals"

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